Knee ARthroplasty versus joint Distraction Study for osteoarthritis (KARDS)

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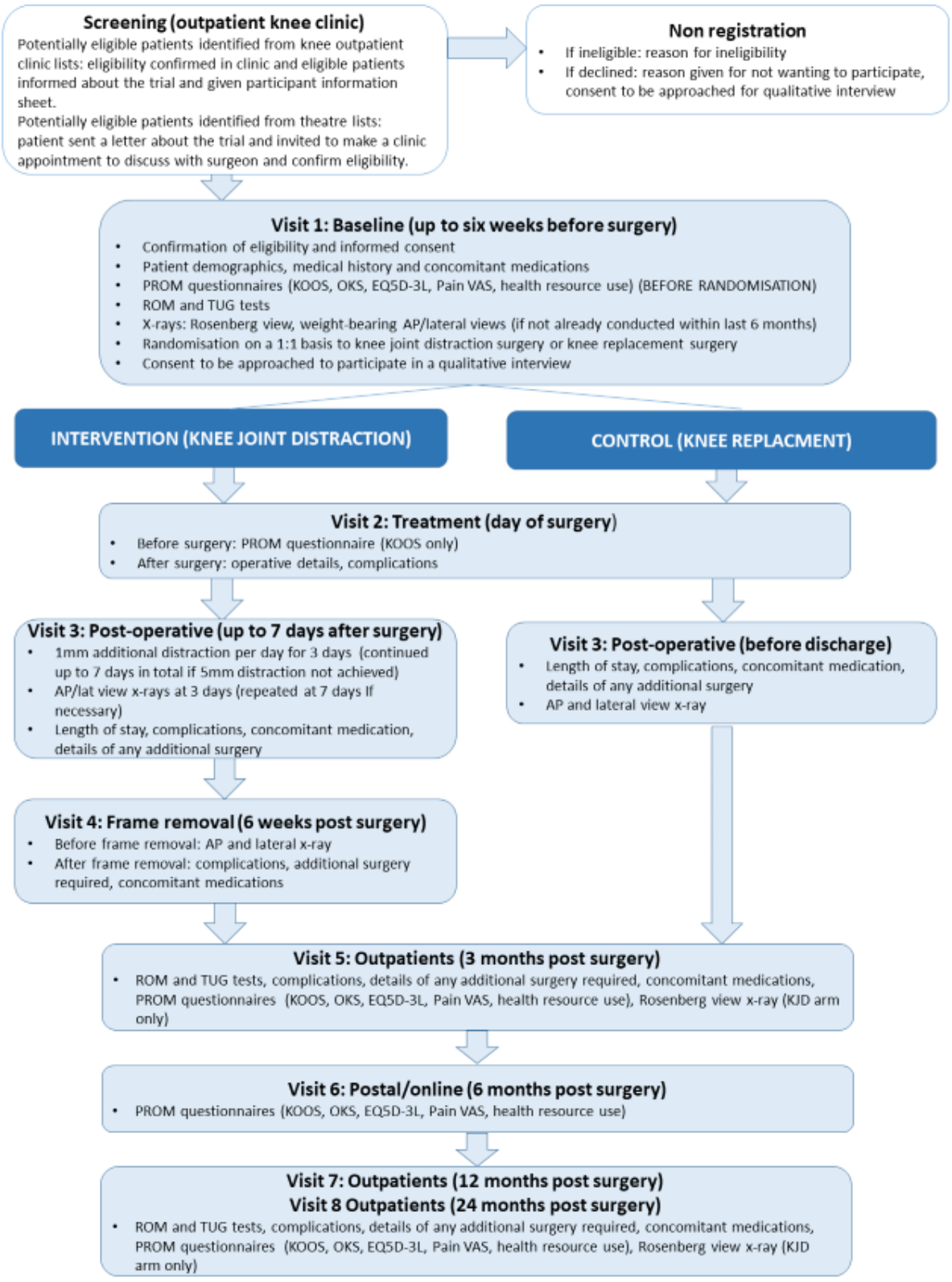
2. CONTENTS PAGE

3. TRIAL SUMMARY

Trial Title	**K**nee **AR**throplasty versus joint **D**istraction **S**tudy for osteoarthritis
Trial Acronym	KARDS
Trial Design	Multi-centre, pragmatic, open-label, two-arm individually randomised controlled non-inferiority trial.
Trial Aim	To investigate the clinical and cost-effectiveness of Knee Joint Distraction (KJD) compared to Knee Replacement (KR).
Trial Objectives	**Primary objective** To examine the clinical effectiveness of KJD compared to KR based on patient reported pain 12 months after surgery. **Secondary objectives** To examine and report: • Patient reported outcomes and quality of life within 24 months after surgery • Objective assessment of knee function • Rates of complications, including infection • The need for further intervention within 24 months after surgery • KJD's potential as a cartilage regenerative therapy • Estimate of short and long term cost-effectiveness • Implementation processes and intervention fidelity • Participant experiences of the trial/interventions and possible facilitators or barriers to wider implementation
Trial Population:	People aged between 18 and 65 with symptomatic knee osteoarthritis, severe enough to warrant unicompartmental or total KR, with intact collateral ligaments and alignment not requiring correction.

Randomisation:	344 patients will be randomised on a 1:1 allocation ratio to KJD (intervention arm) or KR (control arm) based on a minimisation algorithm with random component stratified by delivery unit and osteoarthritis severity.
Trial Interventions:	KJD: Knee joint distracted by 5mm for six weeks using an external fixation frame KR: unicompartmental or total knee replacement
Trial Duration:	All participants will be followed up for 24 months after surgery.
Outcome measures:	**Primary outcome measure** KOOS pain score within 12-months from surgery. **Secondary outcome measures** • Patient reported outcomes and quality of life outcomes • Objective assessment of knee function • Incidence of complications • Joint space width • Cost-effectiveness • Implementation processes and intervention fidelity • Qualitative evaluation of participant experiences

3.1. FLOW DIAGRAM



4. DEFINITIONS

AP	Antero-Posterior
BMI	Body Mass Index
CEAC	Cost Effectiveness Acceptability Curve
CI	Confidence Interval
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
EF	External Fixator
HE	Health Economics
ICER	Incremental Cost Effectiveness Ratio
ITT	Intention to Treat
KA	Knee Arthroplasty
KIDA	Knee Images Digital Analysis
KJD	Knee Joint Distraction
KOOS	Knee Injury and Osteoarthritis Outcomes Score
KR	Knee Replacement
LTRR	Lifetime Risk of Revision
MD	Mean Difference
N	Newton
NHS	National Health Service
NJR	National Joint Registry
NMB	Net Incremental Monetary Benefit
OA	Osteoarthritis
OKS	Oxford Knee Score
PA	Postero-Anterior
PE	Process Evaluation

PIS	Participant Information sheet
PP	Per Protocol
PPI	Public and Patient Involvement
PROMS	Patient Reported Outcome Measures
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
ROM	Range of Motion
STM	Senior Trial Manager
TKR	Total Knee Replacement
TMG	Trial Management Group
TSC	Trial Steering Committee
UKR	Unicompartmental Knee Replacement
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

5. BACKGROUND

Osteoarthritis (OA) is the most common musculoskeletal condition that affects joints, causing pain and joint dysfunction with significant impact on quality of life. In England alone an estimated 8.75 million people aged 45 and over have sought treatment for OA, including 4.1 million with knee OA (1). With rising obesity rates and an ageing population, the number of people presenting with knee OA is increasing (2). In addition, people are presenting with symptoms of knee OA at a younger age and with different expectations as there is a growing tendency to try to stay fit and be more active in later life.

Beyond pain medications and physical therapy strategies, no pharmacological or surgical treatment currently available reliably cures or halts OA. Therefore, patients with knee OA and severe symptoms are typically offered a knee arthroplasty, also known as knee replacement (KR), to relieve pain and improve mobility. KR is a cost-effective and clinically proven technique (3). However, a significant proportion of patients with a KR continue to be dissatisfied with their outcomes. Analysis of the England and Wales National Joint Registry dataset showed that less than 10% of patients after total KR report no problems with their knee whilst a significant proportion have major on-going issues, such as problems with kneeling (57%), persistent pain (20%) and pain on walking (17%) (4). In addition, artificial joints have a finite life span and KRs fail over time, secondary to aseptic loosening, wear or instability, requiring them to be revised. Revision of a KR is complex, costly and associated with higher morbidity, mortality, and inferior outcomes (5–7).

The number of young patients undergoing KR is increasing year on year (7). The risk of failure of KR is disproportionately higher in the young and active. The age adjusted estimates of lifetime risk of revision after KR is 35% in males between 50-54 years of age. These estimates continue to be at least 2 times higher for men and women aged 65 or under as compared to those older than 70 years (7). With improved life expectancy, many of these young patients with KR are likely to spend many more years than previously expected with a revision implant, which are associated with poor outcomes and high costs (7). The risk of re-revision in these cases is significantly higher, and associated morbidity (infection, cardio-respiratory problems, stroke, venous thrombo-embolism) and mortality increases with every subsequent surgical intervention.

The decision to have surgery is largely based on a balance between potential risks and benefits. The James Lind Alliance Priority Setting Partnership (8), a public–patient involvement (PPI) group, has established that the relation between timing of joint replacement and best outcome is one of the most significant concerns for patients with OA. This is of particular importance in determining optimum timing for surgery in patients who are expected to outlive their primary KR. Therefore, the length of time a KR will last (before requiring revision) becomes a major factor in deciding whether to proceed with KR surgery.

The age at which a patient receives a KR is the most important factor affecting both implant survival as well as clinical outcomes, with patients younger than 60 years having the worst clinical outcomes and the highest revision rate (5,7). A combined endpoint analysis including revision, poor function and significant pain has shown the KR success to be as low as 59% at 12 year follow-up in patients younger than 60 years (9). Currently 40% of primary KRs and up to 44% of KR revisions in Europe are performed in patients aged ≤65 years (10). Life expectancy of a 65-70 year old in the UK today is typically projected to be an additional 18 (men) to 21 years (women) (11) and thus will need a well-functioning KR for those many years if performed at the age of 65. The risk of revision KR is <5% if the first KR is performed at around the age of 70 years. A procedure which will delay the KR at least up to the age of 70 is therefore worth considering, provided it does not hamper the ability to undergo a KR at a later stage. There is an increasing and unmet need for alternative treatments for knee OA which will delay or reduce the need for KR.

5.1. RATIONALE FOR THE TRIAL

There is a clear unmet need for a treatment which postpones the time to first KR in the young population (≤65 years) with knee OA, thereby preventing or postponing revision KR (9,10). To bridge this gap in treatment options, there is a need for cost-effective strategies that preserve the joint. Knee joint distraction (KJD) is one such treatment option to address the current problems associated with KR in the younger population. KJD is a joint sparing technique not currently widely used in the UK but has shown good mid-term outcomes in studies conducted in the Netherlands (12–14). It utilises the well-established orthopaedic practice of external fixators for fracture stabilisation, except that the stabilisation is across a synovial joint. KJD harnesses intrinsic joint

repair potential, providing cartilage repair and normalisation of subchondral bone abnormalities (12).

KJD aims at mechanically unloading the damaged tibiofemoral joint surfaces of the OA knee and allowing 6 weeks of biomechanical joint homeostasis by distracting the femur from the tibia by approximately 5 mm. This distraction is achieved and maintained using an external fixator assembly. The mechanical unloading prevents further wear and tear of the articular surfaces and also provides a temporary biomechanical and biochemical environment enabling tissue repair (14). Typical external fixators consist of distraction tubes outside of the leg which are attached to bone pins that are surgically inserted into the femur and tibia and are aligned along to the mechanical axis of the leg, bridging the knee. Bone-pins are positioned extra-articular; outside the area that is involved in primary TKR. This precaution is important to prevent potential infection because of previous KJD treatment. This procedure can be performed in 30-45 minutes. To date, none of the patients receiving TKR after KJD treatment (16.6% at 5 years) suffered from a joint or deep wound infection (personal communication).

KJD for treating knee OA has been shown to be safe and effective in studies carried out in The Netherlands (13,15) but no such studies have been conducted in the UK in an NHS setting. One small trial has suggested KJD to be non-inferior to TKR in function and achieved good patient satisfaction from baseline to 5 years in the Western Ontario and McMaster Universities OA Index (WOMAC) functioning and pain scales (12a,b,c). It has also been shown to be non-inferior to tibial osteotomy in randomized clinical trials (14). KJD was predicted to save over 100 TKRs and ~30 revision KRs over a 20-year period for patients <55 years (16). With a willingness to pay €20,000 per QALY, KJD was shown to be cost effective in >75% in all age groups and >90% in young (<55 years).

KJD could be an alternative therapy to KR for younger patients (≤ 65 years) where there is a large unmet treatment need. However, the current evidence base is small and outside of the UK NHS environment. PPI feedback has indicated that the single most important priority for patients in this age group is retaining their own knee, at the expense of some residual knee pain. If shown to be non-inferior in the NHS setting, KJD could be offered to patients aged 65 and under and thereby enable postponement of KR and further revision surgery.

6. AIMS AND OBJECTIVES

The overall aim of KARDS is to investigate the clinical and cost-effectiveness of KJD compared to KR in the treatment of patients aged 65 years or under. The target population is patients with symptomatic knee OA that is severe enough to warrant KR (unicompartmental knee or total) and who have intact collateral ligaments and leg alignment not requiring correction.

6.1. PRIMARY OBJECTIVE

To examine the clinical effectiveness of KJD compared to KR based on patient reported pain 12 months after surgery.

6.2. SECONDARY OBJECTIVES

To examine and report:

1) Patient reported outcomes and quality of life within 24 months after surgery
2) Objective assessment of knee function
3) Rates of complications, including infection
4) The need for further intervention within 24 months after surgery
5) KJD's potential as a cartilage regenerative therapy
6) Estimate of short and long term cost-effectiveness
7) Implementation processes and intervention fidelity
8) Participant experiences of the trial/interventions and possible facilitators or barriers to wider implementation

7. DESIGN

7.1. TRIAL DESIGN SUMMARY

KARDS is a multi-centre, pragmatic, open-label, two-arm individually randomised controlled non-inferiority trial. The trial has a non-inferiority design based on PPI feedback indicating a strong preference to retain the knee with KJD over KR providing there is no worse knee pain.

A total of 344 participants will be randomised on a 1:1 basis between KJD and KR, stratified by surgical delivery unit and osteoarthritis severity (Section 14).

A hybrid expertise design will be used to account for surgeon expertise in the surgical procedures and potential lack of individual equipoise (Section 8.2).

The trial has an embedded 12-month internal pilot phase (Section 7.2) and process evaluation (Section 16) with selected clinicians, participants and non-recruited patients to evaluate feasibility of recruitment and address any barriers to recruitment. The qualitative process evaluation will assess clinician experience and patient acceptability during the pilot phase and throughout the main trial.

All participants will be followed for 24 months post-surgery (Section 12). The trial will not be blinded to participants, medical staff, or clinical trial staff.

7.2. INTERNAL PILOT

The trial will include a 12 month internal pilot phase to evaluate the feasibility of recruitment within the planned timelines. The target at the end of the internal pilot study is for 16 sites to be open to recruitment and for those sites open for at least 3-months to be recruiting at a rate of 1 patient per month. At this rate, it is estimated that a total of 70 participants will be randomised from 16 sites by the end of the 12 month internal pilot phase. Recruitment rates, dropouts and reasons for non-registration will be assessed.

An independent Data Monitoring and Ethics Committee (DMEC) will meet and will report to the independent Trial Steering Committee (TSC) at the end of the pilot phase, which will subsequently report its recommendations including trial continuation to the funder. Progression considerations will be based on review of: i) recruitment ii) safety iii) qualitative and process evaluations.

8. ELIGIBILITY

8.1. RESEARCH SITE ELIGIBILITY

Each site must complete a feasibility form which verifies that the research site is willing and able to comply with the trial requirements.

Participation of research sites will be dependent upon the following criteria:

1) Site must be able to deliver both procedures
2) Site must have the capacity to recruit at least 12 participants per year.

Research sites will be required to obtain local management approval, return all required essential documentation to the Clinical Trials Research Unit (CTRU) and undertake a site initiation with the CTRU prior to the start of recruitment into the trial.

8.2. SURGEON ELIGIBILITY

Surgeons are eligible to perform KR if they meet the following criteria:

- EITHER a consultant orthopaedic surgeon OR perform the procedure under the direct supervision of a consultant
  and
- Performed at least 10 knee replacements in the past 12 months as the primary surgeon

Surgeons are eligible to perform KJD if they meet the following criteria:

- EITHER a consultant orthopaedic surgeon OR perform the procedure under the direct supervision of a consultant
  and
- Performed at least 10 external fixations as the primary surgeon OR completed a limb reconstruction fellowship

Surgeons performing the KJD procedure will undertake a trial specific training plan as part of the site initiation.

8.2.1. Delivery units

To facilitate the hybrid expertise based design, surgeons are categorised into delivery units. There are two categories of delivery unit based on the interventions the surgeon is authorised to carry out within the trial:

- *Single delivery unit*: Consists surgeons who are authorised to deliver one type of surgery (KJD **or** KR)
- *Dual delivery unit*: Consists surgeons who are authorised to deliver both types of surgery (KJD **and** KR)

A centre is eligible to participate if they have at least one complete delivery unit. A delivery unit is defined as ‘complete’ in the following ways:

- *Single delivery unit*: At least one surgeon authorised to deliver only KJD and at least one surgeon authorised to deliver only KR

- *Dual delivery unit*: At least one surgeon authorised to deliver both KJD and KR.

A mix of delivery units within a centre is acceptable, however movement of surgeons across delivery units is not permitted during the trial.

8.3. PATIENT ELIGIBILITY

As a pragmatic trial, eligibility is designed to be inclusive. Potentially eligible patients will be adults aged ≤ 65 years requiring a unicompartmental knee replacement (UKR) or a total knee replacement (TKR).

8.3.1. Inclusion criteria

1) Age ≥ 18 years and ≤ 65 years at the time of signing the Informed Consent form
2) Symptoms (pain and/or reduced function) severe enough to warrant knee replacement, in the opinion of the treating clinician
3) Pre-operative leg alignment not requiring correction, in the opinion of the treating clinician
4) Intact collateral knee ligaments, in the opinion of the treating clinician
5) Fixed flexion deformity ≤10° of the involved knee

8.3.2. Exclusion criteria

1) Bone density not sufficient to support pins for 6 weeks, in the opinion of treating clinician
2) Isolated patello-femoral OA, in the opinion of the treating clinician
3) Complete joint space obliteration in both medial and lateral tibio-femoral compartments as seen on weight bearing AP knee radiograph
4) A known diagnosis of inflammatory arthritis
5) Presence of a previous joint replacement in any limb
6) Surgical treatment of involved knee within the past 6 months (excluding arthroscopy)
7) Previous knee joint distraction on the involved knee
8) Previously participated in the KARDS trial
9) Weight > 120kg
10) Pregnant or lactating (confirmed by participant)
11) Active cancer (currently diagnosed and under treatment)

12) Unable to complete all trial procedures (e.g. attend follow up visits, complete questionnaires)
13) Unable to provide informed consent (cognitive disorder such as dementia, psychiatric illness)

Eligibility waivers to inclusion or exclusion criteria are not permitted.

9. RECRUITMENT PROCESS

9.1. RECRUITMENT SETTING

Patients will be recruited from secondary care orthopaedic centres following referral by their GP. Sites will be required to have obtained local ethical and management approvals and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

9.2. ELIGIBILITY SCREENING

9.2.1. Identifying and approaching eligible patients

Potentially eligible participants will be identified from orthopaedic outpatient clinics based on their medical records and referral information. Suitability for inclusion into the trial will be assessed according to the eligibility criteria by a member of the attending clinical team.

Potential participants will receive a full verbal explanation of the trial by a participating surgeon or a member of the clinical research team, allowing them the opportunity to ask any questions.

If interested in considering participation, patients will be given a Participant Information Sheet (PIS) to take away with them which will include details of who to contact if they have further questions or to arrange to take part. They will be informed that a member of the research team will contact them to check if they have any questions and/or to confirm they wish to take part.

Potentially eligible participants may also be identified from screening upcoming theatre lists by the attending clinical team. Contact details of identified potentially eligible participants will be provided to the clinical research team (either a participating surgeon or a member of the KARDS clinical research team) who will then send the

patient an invitation letter about the trial on behalf of the treating clinician. If the patients is interested in finding out more about the trial, a clinic appointment will be arranged so they can discuss the trial further with a participating surgeon.

9.2.2. Non-randomisation logs

Participating sites will be asked to complete a non-randomisation log detailing all patients undergoing a knee replacement who have been considered for the trial but have not been randomised into the trial. Documented reasons for ineligibility or declining participation will be closely monitored by CTRU as part of a regular review of recruitment processes, particularly during the initial 12 month pilot phase. Logs will be returned to CTRU on a monthly basis and will collect the following anonymised information:

- Date screened
- Age
- Gender
- Ethnicity
- Reason not randomised: Not eligible/Declined
- If not eligible: Reason(s) not eligible (all exclusion criteria not met should be noted)
- If declined: Reason for not wanting to participate

9.3. INFORMED CONSENT

Following information provision about the trial, all patients must be given the opportunity to discuss the trial with their family and healthcare professions before they are asked whether they would like to take part. Patients will be given as much time to consider their participation in the trial as possible; ideally a minimum of 24 hours, but this will not be imposed if a participant wishes to consent sooner, is fully informed about the trial and has had sufficient time to consider their participation. The right of a patient to refuse consent without giving reasons will be respected.

Assenting patients will be invited to a baseline visit up to 6 weeks before their planned date of surgery. At this visit they will be formally assessed for eligibility and invited to provide written informed consent for their participation in the trial, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent will be obtained by the Principal Investigator (PI) or an appropriate, delegated, healthcare professional (e.g. another participating surgeon or research nurse) who is GCP trained and has been approved by the PI as detailed on the Authorised Personnel Log.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site. The PI must ensure that any person with delegated responsibility for the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

A record of the consent process specifying the date of consent and those present will be detailed in the participant's hospital notes. The original consent form will be filed in the Investigator Site File at the hospital. A copy of the consent form will be given to the participant, a second copy filed in the hospital notes (as per local practice) and a third copy will be returned the CTRU at the University of Leeds.

Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is carried out in a timely manner according to any timelines requested by the CTRU.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment/care.

9.3.1. Timing of consent

Trial consent must be obtained at the baseline visit before any trial specific procedures are undertaken.

9.3.2. Loss of capacity

Loss of mental capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Should this occur it should be reported to CTRU via a withdrawal form with no further trial procedures or data collection occurring from this point. Any data collected up to the point of withdrawal will be kept on record and used in the trial analysis.

9.4. RANDOMISATION

Participants who have confirmation of eligibility and written informed consent will be randomised into the trial by an authorised member of staff at the trial research site.

Participants will be randomised on a 1:1 basis between KJD (Intervention) and KR (control). Randomisation will be based on a minimisation algorithm with random component stratified by delivery unit (Section 8.2.1) and OA severity (Kellgren-Lawrence Grades 2-3 vs. Grade 4 (Appendix 1)) (17).

Since KJD is not a standard technique only some participating surgeons will have the required experience of this procedure. Additionally, some surgeons may not be in individual equipoise despite there being centre equipoise. A hybrid expertise based design (18) where surgeons are categorised into delivery units allows the trial to be feasible and pragmatic.

9.4.1. Timing of randomisation

Randomisation should take place on the same day as the baseline visit, which can be up to 6 weeks before the planned date of surgery. The range of movement and timed up and go tests should be performed and all baseline questionnaires completed BEFORE the participant is randomised (see Section 12 for further details of baseline assessments).

9.4.2. Randomisation process

Randomisation will be performed centrally using the CTRU automated secure 24-hour randomisation service which can be accessed via the web or telephone. For web and telephone randomisation the same site code, authorisation code/site staff email address and PIN used for registration will be required to access the system. The person telephoning or accessing the web address to randomise the participant must have completed the Randomisation CRF available at the time of telephoning/accessing the web as the following information will be required:

- Site code
- Details of intended delivery unit
- Participant details, including initials and date of birth
- Confirmation of informed written consent

- Confirmation of participant's eligibility for the trial
- Confirmation of completion of TUG test and ROM
- Confirmation of completion of baseline participant questionnaires

Direct line for 24-hour randomisation: 0113 343 2290

Web address for 24-hour randomisation: https://lictr.leeds.ac.uk/webrand/

Participants may only be randomised into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log.

After trial randomisation the research site will:

- Add the unique participant ID number to all CRFs and participant consent and contact details forms.
- Return a copy of the completed consent and contact details forms to CTRU
- Book/confirm the surgery and advise the participant of the randomisation allocation and date of planned surgery. Surgery should take place within 6 weeks of the date of randomisation.
- Notify the participant's GP of their participation in the trial using the approved KARDS GP Letter.

Following randomisation, CTRU will email a Participant Randomisation Notification to the research site.

10. INTERVENTION DETAILS

10.1. PRE-OPERATIVE

Pre-operative preparation (e.g. weight loss advice, physiotherapy) will be provided to all trial patients in line with the site's usual protocol for KRs.

10.2. ADMISSION

All trial participants will be admitted on the day of surgery or the previous night and should receive MRSA decolonisation and pre-operative assessment and optimisation as per local practice.

10.3. SURGERY

Surgical consent will be reconfirmed on the day of surgery and participants will be assessed by the clinical team (anaesthetist, and surgeon and/or their assistant) as per standard of care prior to proceeding with surgery.

In the case of single delivery units, patients will be operated on by a surgeon authorised to deliver one type of surgery (KJD or KR as relevant). In the case of dual delivery units, patients will be operated on by the intended surgeon regardless of their randomised allocation.

A surgical manual will be provided detailing the surgical procedures for both interventions and highlighting mandatory components.

10.3.1. Knee joint distraction

A definitive external fixator construct should be used which allows for controlled linear distraction across the knee joint of 5mm along the mechanical axis of the limb. The exact nature of the construct will depend on the equipment available at the site and surgeon preference. A list of permitted devices will be detailed in the surgical manual, and sites wishing to use devices not appearing on this list must provide CTRU with details of their preferred construct during site feasibility for prior approval. All equipment used must be CE-marked and intended to be used for distraction.

During surgery, the external fixation frame should be assembled according to this manual, with a focus on meticulous pin insertion to minimise the risk of complications. Fluoroscopy will be used to assist correct pin placement. Once the assembly is complete, 2mm of axial distraction (measured at frame) should be applied across the knee joint.

The limb should then be cleaned and a final check made for soft tissue tension around fixation elements with further skin releases made as required. Pin-sites should be dressed with an absorbent non-shedding dressing. Clips and bungs are available with various systems to keep these in place and apply gentle pressure.

10.3.2. Knee replacement surgery

Knee replacement surgery will be performed in line with local practice. Surgical steps will vary depending upon type of implant and surgeon preference but mandatory

components will be highlighted in the surgical manual. The surgeon performing the procedure is expected to be familiar with and follow the specific surgical steps for the implant being used as detailed in the instructions for use document provided by the manufacturer.

10.4. POST-OPERATIVE CARE

10.4.1. All participants

Routine general post-operative care will be employed in line with local site protocols. Participants can be mobilized on the first day post op under physiotherapy supervision. Full weight-bearing as pain allows is permitted. Participants can be discharged as soon as they are fit to return home, in line with local practice.

Standardised x-rays (AP and lateral views) will be taken according to a radiography manual which will be provided to sites.

10.4.2. Up to 7 days post operation (KJD only)

A further 1mm of distraction will be applied per day for three days to create a total of 5mm articular distraction at the frame. This can be done in hospital or by the participant at home, following instruction, as preferred. At day 3 the participant will have a standardised AP and lateral x-ray to confirm the distraction at the joint (see radiography manual for further details).

If distraction at the joint is less than 5mm at day 3 the frame will continue to be distracted by 1mm a day until 5mm of distraction at the joint is confirmed radiographically, or up to a maximum of 7 days in total.

10.4.3. Fixator removal (KJD arm only)

External fixators will be removed under general or regional anaesthesia at Week 6 after placement, as detailed in the surgical manual. Standardised AP and lateral x-rays will be taken before the frame is removed, as detailed in the radiography manual.

Participants will be admitted as day case patients with appropriate preparation for anaesthesia according to local protocols. Following administration of anaesthesia, all dressings will be removed. The external fixator assembly will be removed leaving the

pins in place. The pin-sites will be cleaned thoroughly and the pins will then be removed by hand. Pin-sites must be left open and covered with adhesive dressings.

A gentle manipulation under anaesthesia (MUA) to achieve at least 0 to 90 degrees of motion should then be attempted. Once recovered from anaesthesia the participant will be allowed home, usually the same day.

Pin-sites will be kept covered until they have healed and immersion in water avoided. Participants are generally permitted to shower as long as the pin-sites are covered.

10.5. ADDITIONAL INTERVENTIONS

During the course of follow up participants may require further intervention for symptomatic knee OA as per routine NHS practice. Further clinical intervention is permitted for all participants and recorded as part of the trial.

10.6. CONCOMITANT TREATMENTS

Decisions about concomitant medications/treatments for symptomatic knee osteoarthritis will be according to the local medical plan and clinical management.

11. OUTCOME MEASURES

The trial will follow the recommendation to report a range of patient reported outcome measures (PROMs) and clinical experience to observe consistency across measures (19).

11.1. PRIMARY OUTCOME MEASURE

The primary outcome measure is the KOOS pain score within 12-months from surgery.

The Knee Injury & Osteoarthritis Outcomes Score (KOOS) is a patient-administered questionnaire, validated for use in patients with knee OA or knee injury (20). It consists of 5 domains: Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee related Quality of life (QOL). It is recommended as the PROM of choice for assessment of patients with knee OA by the International Consortium for Health Outcomes Measurement. It typically takes 10 minutes to complete. It has been used in many RCTs comparing outcomes of knee OA treatment (21–23). For the purpose of an RCT, KOOS subscale scores are recommended to be

used as the primary outcome (24). A total KOOS score has not been validated and is not recommended.

The primary outcome measure is the KOOS pain component, given pain was indicated by the PPI group as being the most important outcome. In patients with severe knee OA, pain refractory to conservative treatment is the primary indication for a surgical intervention. Knee pain associated with OA typically continues to improve for the first 12 months after an intervention and then plateaus (25). Hence the KOOS, and other outcome measures, will be requested to 24-months post-surgery.

The previous week is the time period considered when answering the questions. Standardised answer options are given (5 Likert boxes: None, Mild, Moderate, Severe, Extreme) and each question is assigned a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each KOOS domain.

11.2. SECONDARY OUTCOME MEASURES

1. Patient reported outcomes and quality of life outcomes

a) **KOOS (At component level)**

KOOS domains (except pain): other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee related Quality of life (QOL).

b) Pain VAS

The pain VAS is a unidimensional measure of pain intensity (26,27), which has been widely used in diverse adult populations, including those with rheumatic diseases (26,28–30). The pain VAS is a continuous scale comprised of a 10cm horizontal length ranging from “no pain” (score of 0) to “pain as bad as it could be” or “worst imaginable pain” (score 100 [100mm scale])

c) **Oxford Knee Score (OKS)**

OKS is a short, reproducible, valid PROM consisting of 12 items which provides an overall scale for assessing outcomes of knee interventions and is sensitive to clinically important changes (31–33). Each question is scored from 0 to 4 with 4 being the best outcome. This method when summed produces overall scores from 0 to 48 which reflects the severity of problems that the respondent has with their knee, with 48 being the best outcome (i.e. least symptoms). It takes approximately

5 minutes to complete the form. Whilst the applicability of the OKS to the general OA population is unclear, it is commonly used for joint replacement registries and is the outcome measure of choice of the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man.

2. *Objective assessment of knee function*

a) **The active range of movement**. Measured using a goniometer at 3, 12 and 24 months, the angles in degrees will be measured with the affected leg fully extended (extension) and fully bent (flexion), to determine the range of movement (i.e. the difference in angles between the two values, extension minus flexion). A flexion deformity will be measured as a positive value and hyperextension will be recorded as negative value.

b) **Timed-up-and-go test**. Time in seconds for the participant to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down.

3. *Incidence of complications*

Intra-operative complications: Complications occurring during the initial trial operative procedure will be recorded.

Post-operative complications*:* Post-operative complications will be recorded and reported by their degree of severity using the Clavien-Dindo classification (Section 13.2.1). Surgical site infection will be categorised based on the Centers for Disease Control and Prevention (CDC) classification and recorded with antibiotics use (34).

Further surgical interventions: defined as any unplanned surgical intervention on the affected knee including management of infection, stiffness or fracture. Primary knee replacement (in the KJD arm) and revision knee replacement (in the KR arm) are considered as further interventions.

4. *Joint space width*

For the KJD group of participants, radiographic assessment of joint space width (an indicator of intrinsic cartilage repair) will be performed using standardised Rosenberg x-ray radiographs (35) to ascertain the structural benefits of distraction. These semi-flexed Posterior Anterior (PA) radiographs of the tibiofemoral joint will be taken under full weight bearing conditions (36a) using a standardised protocol

detailed in the trial radiography manual provided to sites by the trial team. X-rays will be assessed by blinded central review using KneeMorph (MatLab, Release 2015b, The MathWorks, Inc., Natick, Massachusetts, United States.

5. *Cost-effectiveness*

EQ-5D-3L questionnaire

The EQ-5D is a generic PROM of health status assessing five health outcome domains summarised into a single score (www.euroqol.org). The EQ-5D is the most commonly used and best validated assessment tool of health related quality of life(36b). It forms part of the NICE reference case for cost per Quality Adjusted Life Years (QALY) analysis. It is validated for use in OA for all dimensions and all levels. It typically takes 5 minutes to complete the form.

EQ-5D-3L comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems combined across the five dimensions into a 5-digit number that describes the patient's health state.

The EQ-5D VAS scale records the patients' self-rated health on a vertical visual analogue scale from 0 ('Best imaginable health state') to 100mm ('Worst imaginable health state').

Health Resource Utilisation and Private Costs questionnaire

This trial-specific questionnaire will measure participant's reported health care use, days off work and private costs due to knee OA using a bespoke short self-reported schedule adapted from forms already developed at the University of Leeds. Healthcare use includes the number of contacts with clinical staff (occupational health, primary care staff, rheumatologists etc.) and medications as a result of knee OA.

6. *Implementation processes and intervention fidelity*

Quantitative

Treatment fidelity will be assessed on the surgical CRF which will record whether the mandatory components of surgery were performed as detailed in the surgical manual and any deviations explained.

Post-operative x-rays (AP and lateral) will also be returned and assessed by central review.

Qualitative

Outcomes relating to the qualitative evaluation with surgical and clinical staff of intervention processes and qualitative fidelity are described fully in Section 16.

7. *Qualitative evaluation of participant experiences*

Outcomes relating to the qualitative evaluation of participant experiences are described fully in Section 16.

12. DATA COLLECTION

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial. CRFs and participant-completed questionnaires will contain the participant's unique trial number, date of birth, and initials. Clinical data will be collected at baseline, on the day of surgery, up to day 7, week 6 (KJD only), and months 3, 12, and 24 post-surgery. Participant completed data will be collected at baseline, on the day of surgery and at months 3, 6, 12, and 24 post-surgery.

12.1. SUBMISSION OF TRIAL DATA

Participating research sites will be expected to submit original paper CRFs to the CTRU at the University of Leeds and retain copies of all completed CRFs for the trial in the Investigator Site File. Following receipt, the CTRU will contact trial sites to resolve any missing or discrepant data. Any outstanding CRFs will be requested by the CTRU until received or until the data is confirmed as unavailable. All trial x-rays will be transferred to the CTRU using the secure file transfer service. For full details of the imaging requirements and process please refer to the radiography manual.

12.2. SCHEDULE OF CLINICAL ASSESSMENTS / DATA COLLECTION POINTS

TRIAL VISIT	1	2	3	4	5	6	7	8
Time from date of surgery	**≤6 weeks before**	**0**	**Up to Day 7**	**Week 6**	**Month 3**	**Month 6**	**Month 12**	**Month 24**
Time window	**-**	**-**	**-**	**-**	**+/- 4 weeks**	**- 2 weeks + 6 weeks**	**+/- 6 weeks**	**+/- 8 weeks**
Visit type	**Baseline**	**Surgery**	**Post-operative**	**Fixator removal**	**Follow up (clinic)**	**Follow up (post / online)**	**Follow up (clinic)**	**Follow up (clinic)**
Treatment group	**All**	**All**	**All**	**KJD only**	**All**	**All**	**All**	**All**
Confirmation of eligibility	X							
Informed Consent	X							
Patient demographics	X							
Medical history	X							
OA severity (Kellgren-Lawrence grade based on standard AP and lateral x-rays)	X							
Physical examination of knee	X°							
Range of movement using goniometer	X				X		X	X
Timed up and go test	X				X		X	X
Rosenberg view x-ray	X				X^		X^	X^
Weight bearing AP/Lateral view x-rays	X°		X	X^				
Participant completed questionnaires (KOOS, OKS, EQ5D-3L, Pain VAS, Health Resource Use)	X	X*			X	X	X	X
Randomisation	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^				
Complications		X	X	X^	X	X	X	X
Additional knee related surgery		X	X	X^	X	X	X	X
Concomitant medications	X	X	X	X^	X	X	X	X

° If not performed within last 6 months prior to baseline
* KOOS only, up to 1 day before surgery
^ KJD arm only

OKS: Oxford Knee Score
KOOS: Knee Injury and Osteoarthritis Outcome Score

12.3. UNSCHEDULED EVENTS

12.3.1. Withdrawal

Clinicians involved in the trial should not withdraw participants from the trial unless it is harmful (ethically, physically or mentally) for the participant to continue or they pose a risk to staff.

In the event that a participant withdraws their participation in the trial prior to randomisation, no further data is required to be submitted.

In the event that a participant withdraws after randomisation they will be requested to attend follow-up visits and provide follow-up data including participant questionnaires, if they consent to do so.

If a participant explicitly states they do not wish to attend follow-up visits and / or contribute further data to the trial or to complete any further participant questionnaires this should be treated as a withdrawal from the trial.

The PI or delegate must make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for intervention or further involvement in the trial are documented using the Withdrawal Request CRF in order that the correct processes are followed by the CTRU and research site following the withdrawal of consent.

12.3.2. Pregnancy

Any suspected or confirmed pregnancies from the date of randomisation until the end of the follow up at month 24 must be recorded on the Notification of Pregnancy CRF and reported to the CTRU by fax or secure file transfer within **7 calendar days** of the research site becoming aware.

If the suspected or confirmed pregnancy occurs before the date of surgery the operation will not go ahead. It is the responsibility of the treating surgeon to decide what course of action should be taken in relation to ensuring the participant's ongoing treatment outside of the trial protocol.

All other trial procedures can be maintained with the participant's consent. All known pregnancies should be followed up until final outcome.

12.3.3. Death

All deaths occurring between a participant's randomisation day and the last day of follow up (i.e. 24 months post-surgery) must be recorded on the Notification of Death CRF and sent to the CTRU within **7 calendar days** of the site research team becoming aware of the death. Data collected will include but not be limited to:

- Date of death
- Cause of death

12.4. PARTICIPANT COMPLETED QUESTIONNAIRES

Participants will complete a number of health-related quality of life questionnaires (see Section 11). Where questionnaires are completed in clinic, an authorised member of the trial team will check that the forms have been completed fully and will be able to provide clarification only if requested by the participant. Staff will be trained to avoid directing patients in their responses. All questionnaires will be completed during clinic visits except at month 6, when the CTRU will send questionnaires to participants either by post or online according to participant consent and preference. Participants will provide details for the method of contact they consent to and express a preference for contact method on the contact details CRF.

Where a participant has expressed a preference to receive their questionnaires by post only: a second set of questionnaires will be posted to participants if the first set of questionnaires are not returned within 2 weeks.

Where the participant has expressed a preference to receive their questionnaires online: participants will receive an email containing an online link to complete their questionnaires, after which a further email reminder containing an online link will be sent one week after the first email if they have not completed the questionnaires. Where a participant has also given permission to receive postal questionnaires and does not respond to the first two emails, then they will be posted the questionnaires at 2 weeks.

Where the participant has consented to a text reminder: participants will be sent a text reminder confirming that the questionnaires have been posted/ online link sent to them and a further text reminder one week after the first text if the questionnaires have not been returned by post or completed online.

12.5. DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of the last participant's last data item corresponding to the 24 month follow-up time point.

13. SAFETY REPORTING

For the purpose of this surgical trial the safety reporting terms adverse events and serious adverse events have been translated into complications and serious complications.

13.1. GENERAL DEFINITIONS

A **complication** is defined as an untoward medical event in a participant which has a causal relationship with the trial. This includes the trial intervention (KR or KJD surgery) and any subsequent treatment relating to the trial intervention (such as treatment of complications caused by the trial intervention and any trial-specific interventions e.g. the consent process and completion of questionnaires).

An untoward medical event can include:

- any unintentional unfavourable clinical sign or symptom;
- any new illness or disease of the deterioration of an existing condition;
- any clinically relevant deterioration in any clinical tests.

A **serious complication** (SC) is defined as a complication which meets at least one of the following criteria:

- results in death;
- is life-threatening[1];
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability;
- consists of a congenital anomaly or birth defect;
- is otherwise considered medically significant by the Investigator.

[1] Life-threatening refers to an event in which the participant was at risk of death at the time of the event, NOT an event which hypothetically may have caused death had it been more severe.

An **Unexpected Serious Complication** (USC) is a serious complication that is **related** and **unexpected** and will require expedited reporting to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms '**related'** and '**unexpected'** as:

- '**Related':** that is, it resulted from the administration of any of the research procedures. All complications are by definition related to the trial procedures (untoward medical events which are unrelated to the trial procedures are not being collected in this trial).
- '**Unexpected':** that is, the type of event that in the opinion of the investigator is not considered expected. Examples of expected complications are provided in Section 13.2.2; note this is not an exhaustive list.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol Section 13.3 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

13.2. RECORDING AND REPORTING COMPLICATIONS

Information on all complications will be collected for this trial whether volunteered by the participant, discovered by investigator questioning or detected through physical examination or other investigation.

13.2.1. Classification of complications

All post-surgery complications should be graded using the Clavien-Dindo classification scale (37) where appropriate (see Appendix 2).

13.2.2. Expected complications – standard reporting

The following is a list of expected complications related to the administration of any research procedure including pre and post-operative complications associated with either surgical procedure or the use of general anesthetic and any further interventions on the affected knee (but are not limited to):

- Complex regional pain syndrome in the affected leg
- Anaesthesia reactions
- Stiffness in the affected leg needing manipulation under anaesthesia
- Pain in the affected leg
- Neuro-vascular injury in the affected leg

- Compartment syndrome in the affected leg
- Infection needing topical, oral or systemic antibiotics
- Infection needing surgical intervention (details of surgical intervention to be provided on a separate form including the organism identified, treatment given, duration of symptoms and current status)
- Revision surgery in the affected leg
- Failure of external fixator frame or pins (breakage / cut out / loosening) (KJD arm only)
- Myocardial infarction
- Angina
- Pneumonia
- Pulmonary embolism
- Any other cardio-pulmonary event needing further treatment
- Cerebro-vascular accident (stroke)
- Fracture in non-affected limb

All expected complications will be reported from randomisation to end of follow-up on standard CRFs.

As the above complications, including those which fulfil the criteria of seriousness, are expected within the trial population they will not be subject to expedited reporting to the main REC. They will however, be included in the annual safety report provided to the main REC.

13.2.3. All other complications – standard reporting

Information about the incidence and severity of all other complications (this includes all non-serious expected and non-serious unexpected complications) which occur from the date of randomisation to end of follow-up will be recorded on standard CRFs. These events will **not** be subject to expedited reporting requirements.

13.2.4. Serious Complications and Unexpected Serious Complications – expedited reporting

The following (SCs) and USCs occurring within 24 months of surgery are subject to expedited reporting and must therefore be notified to CTRU **within 24 hours** of the clinical research staff becoming aware of the event:

- Symptomatic venous thrombo-embolism
- Osteomyelitis
- Fracture in affected limb
- Death within 6 weeks of surgery

Notifications must be sent to CTRU by fax or secure file transfer using the SC / USC CRF. Once all resulting queries have been resolved the CTRU will request the original form is posted to CTRU and a copy retained at site.

24 hr fax for reporting SC & USCs: 0113 343 7985 or medctkards@leeds.ac.uk

For each SC and USC the following data will be collected:

- Start and end dates (if resolved)
- Full details of complication in medical terms with a diagnosis (if possible)
- Action / intervention
- Outcome
- An identifiable and authorised reporting source (i.e. the signature of the investigator or other medic authorised by the investigator at the reporting research site).

Any follow-up information on SCs and USCs must be faxed or sent by secure file transfer to the CTRU as soon as it is available. Events will be followed up until resolution or a final outcome has been reached. All USCs will be reviewed by the Chief Investigator (CI) and will be subject to expedited reporting to the Sponsor and the REC

by the CTRU on behalf of the CI in accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs) and Sponsor requirements.

13.2.5. Untoward medical events unrelated to the trial – not reportable

It is anticipated that there will be minimal additional risks associated with the interventions in this trial. Participants treated may have co-morbidities and in recognition of this, untoward medical events will only be reported if they are classified as related to trial procedures (including the intervention and related procedures or trial-specific procedures such as consent and questionnaire completion).

13.3. SAFETY REPORTING RESPONSIBILITIES

Principal Investigator (PI) (i.e. lead trial clinician at each recruiting research site or appropriate clinical individual identified in the APL)

1. Checking for complications during admission and follow-up, including using medical judgement in assigning:

- Causality, i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
- Seriousness
- Expectedness

3. To ensure all SCs and USCs up to 24 months are recorded and initially reported to the CTRU within 24 hours of the research site team becoming aware and to provide further follow-up information as soon as available.

4. To report SCs and USCs to the CTRU in-line with the protocol.

5. To report USCs to local committees in line with local arrangements.

Chief Investigator (CI) (or nominated individual in CI's absence)

1. Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment.

2. Undertake review of SCs and USCs. In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the main REC.

Clinical Trials Research Unit (CTRU)

1. Expedited reporting of USCs occurring within 24 months post-surgery to the REC and Sponsor according to HRA, CTRU SOPs and Sponsor timelines.

2. Preparing annual safety reports to the REC and periodic safety reports to TSC and DMEC as appropriate.

3. Notifying Investigators of SCs and USCs which compromise participant safety.

Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues. See Section 21.2.2 for further detail about the responsibility of the TSC.

Data Monitoring & Ethics Committee (DMEC)

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. See Section 21.2.3 for further detail about the responsibility of the DMEC.

14. STATISTICAL CONSIDERATIONS

14.1. STATISTICAL ANALYSIS

A full statistical analysis plan (SAP) will be in place prior to any comparative analyses according to guidelines (38). All analyses and patient populations will be predefined in the SAP. Both intention to treat (ITT) and per protocol (PP) analyses have biases so neither are taken as a ‘gold standard’ for non-inferiority trials but can make critical differences to the results of a trial (39). The ITT population includes all randomised patients. The PP population includes all patients who received their randomised intervention. At the time of the final analysis, KARDS will be analysed and reported according to CONSORT extension for Non-Inferiority and Equivalence Randomized Trials (40). Trial outcomes will be analysed primarily for the PP population and repeated, for sensitivity reasons, for the ITT population.

ANALYSES OF THE PRIMARY OUTCOME MEASURE

Adjusted estimates of the treatment effect will be estimated from multivariable regression modelling of the KOOS pain score at 12 months. Statistical significance of non-inferiority of KJD relative to KR will be based on a 2-sided likelihood-based test with a type 1 error of 2.5% in both tails, assuming KOOS pain scores (or transformed scores if appropriate) are normally distributed and adjusted by baseline score at the time of randomisation and stratification factors (delivery unit and OA severity). If the 95% confidence interval for the absolute difference in means between KJD and KR lies entirely below or includes the non-inferiority boundary (see Section 14.2) then there would be insufficient evidence to reject the null hypothesis that KJD is inferior to KR. Conversely, if the 95% confidence interval lies entirely above the non-inferiority boundary then there would be evidence to reject the null hypothesis and conclude KJD is non-inferior to KR. Further modelling will include confounders of age and BMI, observing and addressing non-linearity through use of fractional polynomial transformation. Secondary analyses of the primary outcome measure will be considered. If non-inferiority is demonstrated and KJD appears superior to the KR, based on estimated effect and CI, statistical significance for superiority will be calculated based on an ITT analysis with similar modelling strategy. A secondary analysis of the primary outcome measure will be based on random effects multilevel modelling to account for the nested and longitudinal structure of the data over the full 24 months follow-up.

ANALYSES OF SECONDARY OUTCOME MEASURES

Analysis of PROMs (KOOS components, OKS, Pain VAS and EQ5D-3L) will focus on reporting the pre-specified dimensions of the individual questionnaires. Questionnaire responses will be combined and transformed into dimension scores, according to scoring manuals where these exist, presented graphically and longitudinally. Standardised area under the curve statistics will be compared across treatment groups as an analysis conditional on patient survival.

Range of motion and timed up and go functional assessments will be reported descriptively.

The number of complications, specifically infection, will be reported as unique events and unique patients experiencing events. Joint survival is defined as time from surgery to date of additional secondary procedure, specifically knee replacement/revision knee replacement, or date of censor at patient last follow-up. Joint survival will be estimated using the method of Kaplan and Meier and presented graphically with 12 and 24 month survival estimates and risk (hazard ratio) of additional treatment in KJD as compared to KR, in the ITT population. Global quality of life (QoL) collected as part of the EQ5D-3L may be used in a quality adjusted analysis to analyse QoL and time to secondary procedure simultaneously. Radiographic assessment of joint space width, as an indicator of intrinsic cartilage repair, over a two-year period will be reported descriptively in the KJD group.

EXPLORATORY ANALYSES

Planned exploratory descriptive subgroup analyses will be carried out by delivery unit, type of KR (partial/total), type of pin (hydroxyapatite coated/not) and baseline functioning (poor/better). Tests of heterogeneity of treatment effects across subgroups (not treatment effects within subgroups) may be appropriate.

MISSING DATA

Missing outcome data may be imputed dependent on level of missing-ness and reasons for missing-ness assessing the assumption of missing at random. Sensitivity analyses will report under different assumptions about the missing data. The impact of surgical experience is expected to be minimal; however, sensitivity analyses may be conducted to investigate any impact of surgeon experience on estimates of treatment effect (41).

INTERIM ANALYSES

Interim analyses will be conducted on an annual basis for presentation to the DMEC who will monitor primarily safety outcomes and data quality as well as the underlying assumptions of the statistical design (specifically variability on the primary outcome measure). The DMEC will also review key baseline characteristics (e.g. pain) and stratification factors to ensure balance. Analyses will be agreed and documented upfront by the independent DMEC members. No formal guidelines for stopping the trial early are in place since no formal planned interim analysis of the primary outcome measure is planned (precluded by the follow-up and recruitment timelines).

14.2. SAMPLE SIZE

Sample size and power calculations are based on a non-inferiority hypothesis for the primary outcome measure. Secondary outcome measures are not powered. The statistical design is based on a distribution-based method informed by data from the previous trial (16), clinical co-applicant experience and consensus, reported recommendations of minimally important differences in knee disease and feedback from the PPI focus group. A median 12-point credible minimal difference (range 4 to 20) for patient reported KOOS pain has been recommended (19) and 13-points for patients with knee OA (42). This is supported by patients who report they would accept a 10-15% (translated to 10-15 points) increase in pain to retain their knee. Based on this consensus for a minimally important difference, the non-inferiority threshold is defined to be at least 33% less at a threshold of 8. Previous observational studies of KOOS pain have reported variability (SD) from 15 to 21 (3,43–45).

A one-sided significance of 2.5% is used which allows two-sided 95% confidence intervals to be presented. The target recruitment is based on demonstrating non-inferiority within a limit of 8 points. Ignoring drop-out within 12-months, 146 patients recruited to each group would have 90% power to demonstrate non-inferiority within a threshold of 8 points and variability assumed SD=21. Allowing for 15% dropout, the target is inflated to 172 patients in each group resulting in an overall recruitment target of 344 patients. The underlying assumptions of the statistical design will be monitored by the DMEC.

No sample size adjustment has been made to accommodate surgeon learning curve since external fixation is a common procedure which orthopaedic surgeons are frequently required to do for trauma.

15. ECONOMIC EVALUATION

A within trial cost-effectiveness analysis within 24-months will be conducted adopting the perspective of the NHS and Personal Social Services. Costs and outcomes occurring beyond 12 months will be discounted at 3.5%. The primary outcome is Quality Adjusted Life Years (QALYs). The proposed methods for the economic evaluation follow the NICE reference case (46).

Health utility values will be estimated through administration of the EQ-5D-3L. Unit costs for health service resources will be obtained from national sources (e.g. Personal Social Services Research Unit [PSSRU] and NHS Reference Cost). The intervention cost will include theatre time, knee components used during the primary admission and during any knee-related readmissions or revisions.

The differences in mean costs and effects will be presented using incremental cost effectiveness ratio (ICER). Net incremental monetary benefit (NMB) will also be computed. The level of sampling uncertainty around the ICER will be determined using a nonparametric bootstrap to generate 10,000 estimates of incremental costs and effects. Bootstrapped estimates will be plotted on the cost-effectiveness plane to illustrate the uncertainty surrounding cost-effectiveness estimates (47). Bootstrapped estimates of cost and effects will also be used to compute the probability that each intervention is cost-effective for a range of cost-effectiveness thresholds. The results will be presented as cost-effectiveness acceptability curves (CEAC) (48).

In order to assess the long-term cost-effectiveness of KJD compared to KR, a decision analytic cost-effectiveness model will be used to estimate the likely impact on costs and benefits over 20 years. The model will be constructed and described in line with best practice (46). Data to populate the model will be derived from three sources:

1. The literature

2. Ongoing follow-up studies and clinical trials of Knee Joint Distraction as coordinated by UMC Utrecht (currently N=174 patients in follow-up with max 10 year follow-up, 105 started end 2017)

3. Publicly available UK orthopaedic registry data which will provide transition probabilities on knee replacement initial effects and longer-term effects.

Parameter uncertainty will be addressed using probabilistic sensitivity analysis. The distribution of expected costs and effects will be provided and the probability that the intervention is cost-effective given a range of willingness to pay thresholds will be represented via CEACs.

16. PROCESS EVALUATION

Knee joint distraction is a complex intervention that is not currently used widely in the UK, and delivering this intervention in the context of a trial is likely to present challenges both in terms of recruitment and treatment delivery. The trial will therefore include an integrated process evaluation (PE) to identify barriers in order to maximise recruitment possibilities, as well as identify any challenges experienced of maintaining the integrity of the interventions to minimise variation in intervention delivery. This predominantly qualitative study will be conducted in two key phases i) internal pilot phase and ii) main trial phase.

16.1. PHASE 1: INTERNAL PILOT PHASE

A formative process evaluation will be undertaken during the internal pilot in the first 10 sites open to recruitment. The primary aim of this phase is to maximise recruitment into the trial and identify / minimise variation in intervention delivery that could affect outcomes.

The three objectives are:

1. To document the various care pathways at individual sites that potential participants are exposed to as they consider entry to the trial (context);
2. To engage with key stakeholders (surgeons, recruiting staff, admin staff and patients) at sites to understand their experiences of recruitment;
3. To engage with the surgical teams and explore their perceived facilitators or barriers to delivering the surgical interventions as per the protocol.

16.1.1. Methods

<u>1 – Clinical/research team interviews</u>

Staff involved in the trial at each site will be invited by the qualitative researcher to take part in one or more short structured interviews and discussions to allow free expression of ideas. This will include all key stakeholders (e.g. the PI, other

participating surgeons, research nurses and any other staff involved in the recruitment and delivery of the study at the site). At least one surgeon and two members of recruiting staff will be interviewed at each site.

The aim is to visit each site twice during the internal pilot phase to conduct interviews face to face. The first visit will be arranged around the time the site opens to recruitment, which may be up to three months before the first participant is treated. At this visit the interviews will focus on understanding the site's care pathway and staff's perceptions of the recruitment processes and delivery of the interventions. The second visit will be towards the end of the internal pilot phase and will focus on understanding the site's experience of recruiting to the trial and delivering the interventions. Interviews will be recorded and transcribed for analysis. Transcripts will be anonymised.

2 – Participant interviews

During consent to the main trial all participants will be informed about the qualitative research and given a qualitative interviews information sheet. They will be told that a researcher may contact them to discuss their trial experiences and it will be explained that this is entirely voluntary and will not affect their clinical care or participation in the trial. Their willingness or not to be contacted by the PE researcher will be recorded on the main consent form. Contact details for participants who indicate that they may wish to be involved in an interview will be sent to the PE research fellow (RF) by the CTRU.

In this formative evaluation phase the aim will be to interview all participants at the 10 pilot sites who are willing to take part and who have reached their time of discharge before the end of the internal pilot. Interviews will be conducted by telephone as semi-structured interviews and will explore their involvement in the trial from consent through to operation and (depending on timing of the interview) recovery. Informed consent will be confirmed verbally at the start of the interview and documented by the interviewer on a record of consent form. Interviews will be recorded and transcribed for analysis. Transcripts will be anonymised.

3 – Non-participant interviews

Eligible patients who decline to take part in the trial will also be offered the option to take part in a telephone interview to understand their decision in choosing not to participate in the trial. A process evaluation information sheet will be provided and it will be explained that this is entirely voluntary, will not affect their clinical care and that there will be no pressure to change their decision. Patients who indicate they would be willing to be interviewed will be asked for written consent for their contact details to be passed on by the CTRU to the PE RF who may contact them to arrange an interview. Interviews will be conducted by telephone as a one off interview, recorded and transcribed for analysis. Informed consent will be confirmed verbally at the start of the interview and documented by the interviewer on a record of consent form. Transcripts will be anonymised.

16.1.2. Data analysis and reporting

All data collected during the formative process evaluation will be analysed in a continuous ongoing process. Findings will be discussed at the Trial Management Group regularly throughout the internal pilot phase so appropriate actions can be discussed and changes implemented as required.

16.2. PHASE 2: MAIN TRIAL (POST INTERNAL PILOT PHASE)

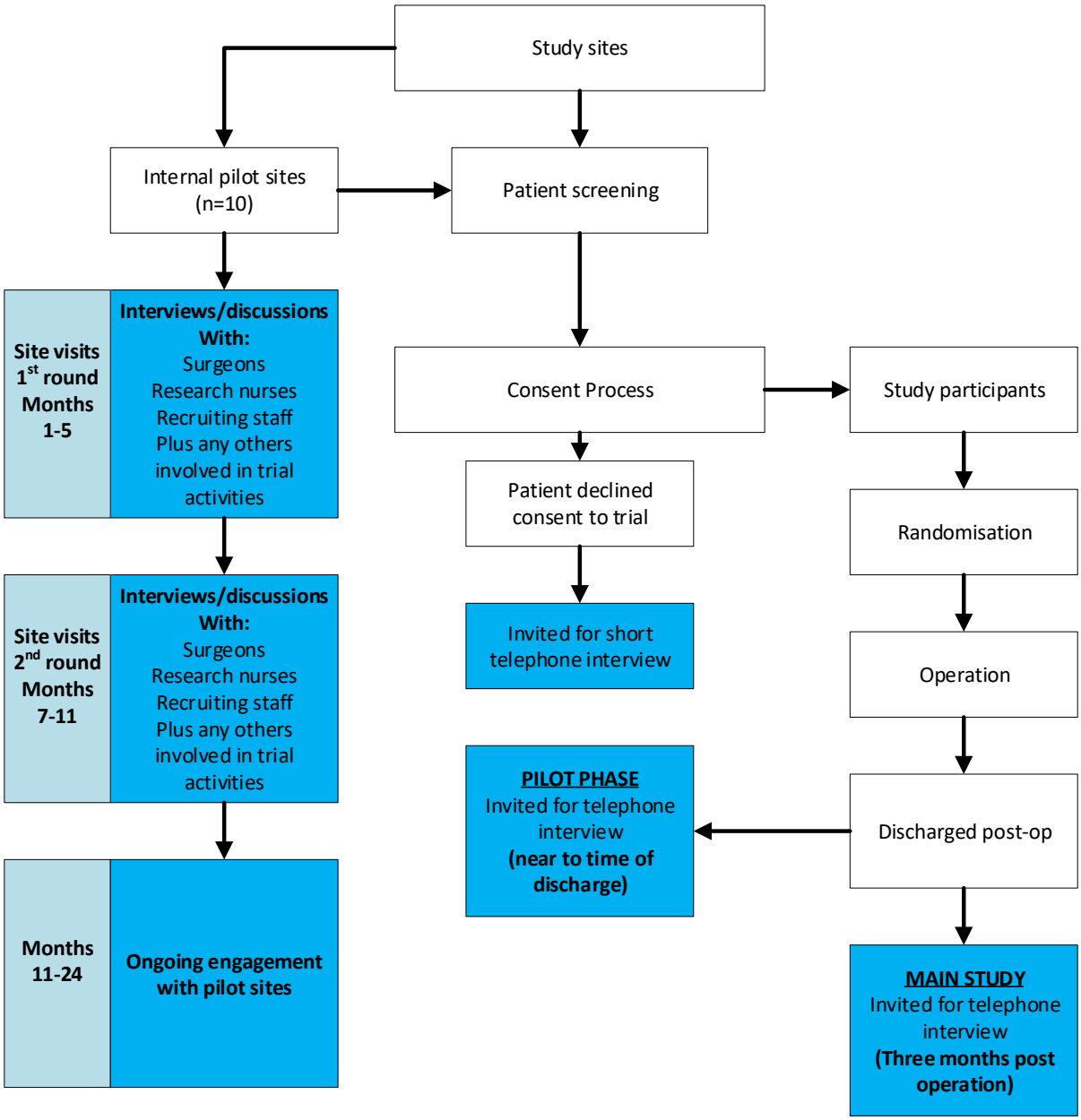
Following completion of the 12 month pilot, further participant / non-participant interviews will be conducted during the main trial to gain a greater understanding of the patient experience in the trial. This phase of the process evaluation will take place in the second year of recruitment.

16.2.1. Methods

Randomised participants will be offered the option to take part in a qualitative interview. A simple sampling matrix will be used to select a purposive sample based around age and gender and balanced across treatment arms. A minimum of 54 participants from a minimum of 10 sites across the two randomised groups will be interviewed. Interviews will take place at 3-months post-surgery and will be arranged and conducted in the same way as the internal pilot interviews (see Section 16.1.1).

Eligible patients who decline to take part in the trial and have provided written informed consent to take part in a telephone interview will also be interviewed as outlined in Section 16.1.1.

16.3. PROCESS EVALUATION FLOWCHART



16.4. DATA ANALYSIS AND REPORTING

Interview data will be analysed using thematic content analysis to identify patterns or themes (49), using coding of audio-transcript recordings, adopting the framework method described by Ritchie and Spencer and Pope et al (46,50). Normalisation Process Theory will be used as a theoretical framework to explore and explain the extent of implementation of the intervention (51–53).

The software package NVivo 12 will be used to manage the data and facilitate this process. Researcher bias will be minimised through regular crosschecking of the data and findings by the members of PE research team. Quotes will be used as exemplars of key themes.

Coded interviews, observations and a full record of issues raised will be discussed in detail at the TMG and summarised for the oversight committees. Good practice at sites will be shared with other recruiting sites.

17. DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be requested until it is received, confirmed as not available or the trial is at the analysis stage. Missing data items will not be requested from participants over and above the principles laid out in Section 12.4. The CTRU and Sponsor reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU or Sponsor. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

17.1. CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

17.2. QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 (for studies conducted in Scotland), and through adherence to CTRU Standard Operating Procedures (SOPs).

17.3. SERIOUS BREACHES

Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the National Research Ethics Service SOP). A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

17.4. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013, Informed written consent will be obtained from the patients prior to randomisation into the trial. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

Ethical approval will be sought through the Health Research Authority (HRA). The trial will be submitted to and approved by a REC, the HRA and the appropriate Site Specific Assessor for each participating research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

18. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the Data Protection Act 2018 and operationally this will include:

- Consent from participants to record personal details including name, date of birth, address (including postcode), email address and telephone/mobile phone number, NHS number, hospital number, GP name and address.
- Participant name, date of birth, NHS number, contact details and GP name and address will recorded by sites at the randomisation visit (subject to consent) and retained by them.
- Consent from participants for a letter to be sent to their GP to let them know they are taking part in the trial.
- Consent from participants for the CTRU to receive a copy of their consent form, contact details and NHS number to facilitate data collection for future research.
- Consent from participants for their radiograph images to be sent via electronic transfer to the CTRU and other named members of the TMG (with identifiers trial number, initials and date of birth only; the participant's name should be obliterated by site before sending).
- All data collection forms that are transferred to or from the CTRU will be coded with a trial number and two participant identifiers, usually the participants' initials and date of birth. The consent forms will be sent to the CTRU and stored separately from the clinical data.
- Consent from participants to allow their name, date of birth, NHS number to be sent to the National Joint Registry for long term follow up of clinical outcomes (optional).
- Consent from participants for the qualitative researcher at the University of Warwick to receive their name and contact details (optional).
- Appropriate storage, restricted access and disposal arrangements for participating research site staff, and participant personal and clinical details.

- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans), the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

18.1. ARCHIVING

At the end of the trial, all data held by the CTRU and the University of Warwick will be securely archived in line with the Sponsor's procedures for a minimum of 15 years.

Research sites are responsible for archiving all trial data and documents (Investigator Site File and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

19. STATEMENT OF INDEMNITY

This trial is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the trial.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Therefore, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements under this duty of care.

20. TRIAL ORGANISATIONAL STRUCTURE

20.1. INDIVIDUALS AND INDIVIDUAL ORGANISATIONS

Chief Investigator (CI) – As defined by the NHS Research Governance Framework, the CI is responsible for the design, management and reporting of the trial.

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU) – The CTRU will have responsibility for conduct of the trial in accordance with the NHS Research Governance Framework (RGF) and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs and the RGF, including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support main REC, Site Specific Assessment and NHS Permissions submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses and reporting.

The University of Warwick will be responsible for the process evaluation qualitative research.

20.2. OVERSIGHT/TRIAL MONITORING GROUPS

20.2.1. Trial Management Group (TMG)

The TMG, comprising the CI, CTRU team, trial co-applicants and other nominated external members involved in the trial are responsible for the clinical set-up, on-going management, promotion of the trial and for the interpretation and reporting / publication of results. Specifically the TMG will be responsible for

- Protocol completion,
- Database and CRF development,
- Obtaining approval from the main REC and supporting applications for Site Specific Assessments,

- Completing cost estimates and project initiation,
- Nominating members and facilitating the TSC and DMEC,
- Reporting of serious complications and Unexpected serious complications,
- Monitoring of screening, recruitment, treatment and follow-up procedures,
- Auditing consent procedures, data collection, trial end-point validation and database development.
- Developing and implementing a Trial Monitoring Plan detailing any on-site monitoring

20.2.2. Trial Steering Committee (TSC)

The independent TSC have overall responsibility for the external oversight of the trial. The TSC will provide overall monitoring of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. The TSC meeting will be conducted to an agreed TSC Charter and members will be provided with reports prepared by CTRU. The independent committee will meet at least annually and will consider recommendations made by the independent DMEC.

20.2.3. Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will review the safety of participants in the trial by reviewing interim data during the recruitment phase The DMEC meeting will be conducted to an agreed DMEC Charter and members will be provided with reports prepared by CTRU. The DMEC meeting will consist of open and closed sessions to discuss aggregate data and, in the closed session, data presented by randomised group. The DMEC will review the underlying assumptions of the statistical design to ensure the trial remains adequately powered. The Committee will meet annually as a minimum and make recommendation regarding continuation, specifically following the internal pilot phase to the TSC.

21. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment. The success of the trial depends upon the collaboration of all investigators. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship or contributor-ship. Requirements for authorship state evidence of substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, and relevant senior CTRU staff will be named as authors in any trial related publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, outcome data will not be released prior to the first publication of the analysis of the primary outcome measure, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary outcome.

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23. APPENDICES

APPENDIX 1: KELLGREN LAWRENCE GRADE

GRADE	DEFINITION
GRADE 0	No radiographic features of osteoarthritis
GRADE 1	Possible joint space narrowing (normal joint space is at least 2 mm at the superior acetabulum)[7] and osteophyte formation
GRADE 2	Definite osteophyte formation with possible joint space narrowing
GRADE 3	Multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity
GRADE 4	Large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity

APPENDIX 2: CLAVIEN-DINDO CLASSIFICATION OF COMPLICATIONS

GRADE	DEFINITION
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III Grade IIIa Grade IIIb	Requiring surgical, endoscopic or radiological intervention Intervention not under general anesthesia Intervention under general anesthesia
Grade IV: Grade IVa Grade IVb	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management Single organ dysfunction (including dialysis) Multi organ dysfunction
Suffix “d”	If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain haemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.