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Robotic-assisted surgery and kinematic alignment in total knee arthroplasty (RASKAL study): a protocol of a national registry-nested, multicentre, 2×2 factorial randomised trial assessing clinical, intraoperative, functional, radiographic and survivorship outcomes

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ABSTRACT

Introduction Robot-assisted surgery (RAS) and kinematic alignment (KA) are being increasingly adopted to improve patient outcomes in total knee arthroplasty (TKA). There is uncertainty around the individual or combined effect of these concepts compared with computer-assisted surgery (CAS) and mechanical alignment (MA), respectively. This study aims to assess the effectiveness of RAS, KA or both to improve clinical outcomes, functional measures, radiographic precision and prosthetic survivorship when compared with current gold standards of surgical care.

Methods and analysis A national registry-nested, multicentre, double-blinded, 2×2 factorial, randomised trial will be undertaken with 300 patients undergoing primary unilateral TKA performed by 15 surgeons. The primary outcome will be the between-group differences in postoperative change over 2 years in the mean Knee injury and Osteoarthritis Outcome Score (KOOS-12), comparing first, RAS to CAS as its control, and second, KA to MA as its control. Secondary outcomes will include other knee-specific and general health patient-reported outcome measures (PROMs), intraoperative pressure loads as a measure of soft tissue balance, 6-month postoperative functional outcomes, radiological precision using CT imaging, complications and long-term prosthetic survivorship. The contribution of each patient's unique coronal plane alignment of the knee phenotype to primary and secondary PROMs will be investigated. OMERACT-OARSI criteria and Patient Acceptable Symptom State outcome score thresholds for the KOOS-12 and Oxford Knee Score will be used in secondary analyses. Primary intention-to-treat and secondary per-protocol analyses will be performed. Statistical analysis will include a generalised linear mixed model for repeated measures for continuous KOOS-12 scores. Kaplan-Meier estimates with adjusted HRs of implant survivorship will be calculated.

Ethics and dissemination Ethics approval was obtained from Sydney Local Health District-Royal Prince Alfred Hospital (Approval X20-0494 and 2020/ETH02896 10.24/DEC20). Results will be submitted for publication in a peer-reviewed journal and presented in national, state and international meetings.

Trial registration number ACTRN12621000205831.

Strengths and limitations of this study

- ⇒ Robotic-assisted surgery will be compared against computer-assisted surgical navigation, which is the current gold standard in knee alignment.
- ⇒ Kinematic alignment will be compared with mechanical alignment with standardisation of other surgical processes.
- ⇒ The 2x2 factorial study design allows for assessment of potential interactions between two topical techniques in total knee arthroplasty.
- ⇒ The trial nested within an established large national joint replacement registry will allow for unique monitoring of long-term prosthetic survivorship.
- ⇒ Potential limitations are the exclusion of moderate to severe coronal and sagittal plane deformities, the absence of a conventional instrumentation arm, the reliance on preoperative assessment with a two-dimensional-imaging modality for coronal plane alignment of the knee assessment and finally the use of restricted kinematic alignment which may incompletely balance some knees.

INTRODUCTION

Total knee arthroplasty (TKA) remains the gold-standard treatment for end-stage osteoarthritis (OA) of the knee.[1] However, approximately 18% of patients report some level of dissatisfaction following TKA.[2–4] Patient dissatisfaction may result from inappropriate soft tissue balance resulting in knee stiffness, instability,

asymmetric joint laxity and patellofemoral maltracking.[5–10] In an attempt to improve patient outcomes, two significant surgical developments with independent aims have been adopted over the last decade: robotic-assisted surgery (RAS) and kinematic alignment (KA).

RAS was introduced with the aim of increasing the precision of prosthetic alignment and has subsequently evolved to include soft tissue balancing algorithms and haptic cutting boundaries to reduce intraoperative soft tissue trauma.[11–14] Drawbacks to RAS include increased costs, potential for surgical complexity and increased operating times during the learning curve. There is sparse and contradictory evidence regarding the effect of RAS on clinical outcomes.[15–20] Previous studies have only compared RAS to conventional guides and most involved first-generation robots which are no longer in use.[21–27] The predecessor to RAS, computer-assisted surgical navigation (CAS), remains the gold-standard method to reduce alignment outliers. It results in lower revision rates in patients under the age of 65 when compared with conventional instrumentation.[28 29] Hence, justification for the routine adoption of RAS should be based on high quality comparisons with CAS, which have not yet been performed.

A separate major development has been the KA technique. This strategy aims to restore each patient's constitutional knee anatomy.[30] It contrasts the mechanical alignment (MA) method which systematically aligns implants perpendicular to the femoral and tibial mechanical axes with compensatory femoral component external rotation, irrespective of native anatomy. MA is the gold-standard alignment method and has been considered advantageous by providing a loading pattern that may be more resilient to premature prosthetic failure. However, improvements in polyethylene durability and a better understanding of the contribution of postoperative limb alignment to survivorship has allowed a shift to a more individualised alignment approach. KA has been shown to more closely restore native soft tissue laxities, restore physiological gait patterns, reduce the requirement for soft tissue releases and minimise bone resections when compared with MA.[31–46] It is theorised that these benefits may provide the patient with a less 'prosthetic-type' feeling knee compared with the MA.

To date, studies comparing KA to MA have used various instruments including CAS, intraoperative callipers and conventional guides,[31 32 34 47] all of which have varying degrees of precision.[29 48 49] A meta-analysis of randomised trials found no statistically significant difference in patient-reported outcome measures (PROMs) when KA was compared with MA, with long-term outcomes remaining unknown.[50] Further, studies examining the effectiveness of KA have not considered each individual's unique coronal plane alignment of the knee (CPAK) phenotype[30] when determining which patients may benefit most from this intervention versus MA. The final concern with KA is premature implant failure, due to the potential for outliers from target alignments, especially when using techniques with lower degrees of precision.

Adoption of both of these new techniques is rising, with 21% of American Association of Hip and Knee Surgeons surveyed in 2018 using robotic-assistance and 10% using KA.[51] Given the significant expenditure invested in RAS, along with increasing adoption of KA, analysis of patient outcomes and implant survivorship is required. To the best of our knowledge, there have been no appropriately designed, randomised trials undertaken to answer these important and inter-related questions.

The purpose of this research is to assess the effectiveness of RAS, KA or both to improve clinical outcomes, functional measures, radiographic precision and prosthetic survivorship when compared with the current gold standards of surgical care. The primary study aims are to determine in patients undergoing primary, unilateral, TKA for knee OA:

1. If there is a clinically important difference between RAS and CAS, as measured by changes in Knee injury and Osteoarthritis Outcome Score 12 (KOOS-12)[52] over 2 years.
2. If there is a clinically important difference between KA and MA, as measured by changes in KOOS-12 over 2 years.

Secondary study aims include assessing the effectiveness of RAS and KA other knee and general health-specific PROMs, tibiofemoral compartment pressure loads, functional parameters, radiographic alignment, complication rates and implant survival. The interaction between the two treatment types will be explored along with consideration of preoperative CPAK phenotype when measuring primary and secondary outcomes.

The primary null hypotheses are that in patients with knee OA undergoing primary unilateral TKA, there will be no between-group difference in the KOOS-12 over 2 years, when comparing RAS to CAS, and when comparing KA to MA.

METHODS AND ANALYSIS

Study design

We will conduct a multicentre, blinded, randomised, 2×2 factorial (RAS vs CAS; KA vs MA), trial in 300 TKA patients. The study will be nested within the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) using the RAPID (Real time Automated Platform for Integrated Data) platform.[53] Patients, assessors, radiographers and statisticians will be blinded to treatment allocation for the study duration. The protocol has been endorsed by the executive committees of the Australian Society of Arthroplasty and the Australian Knee Society. The 2013 Standard Protocol Items: Recommendations for Interventional Trials Checklist is provided in online supplemental 1.

Fifteen surgeons from eleven Australian hospitals (community and academic centres) will be a part of the Surgeon Workgroup and will each perform a minimum of 20 TKAs. In order to participate, surgeons must have undergone robotic training and have performed a minimum of 10 RAS

and 10 CAS TKAs to mitigate any learning curve effect.[25 54] All patients will receive a fully cemented, cruciate-retaining prosthesis with patellar resurfacing using the Triathlon Total Knee System. Knees will be aligned with either a robotic cutting arm (MAKO SmartRobotics, Stryker, Kalamazoo, Michigan, USA) or optical computer-assisted navigation (Precision-3, Stryker, Kalamazoo, Michigan, USA). If the posterior cruciate ligament (PCL) is deemed to be lax or incompetent intraoperatively, then a cruciate-stabilised (anterior-lipped) or posterior-stabilised insert may be used. All patients will be included in the primary intention-to-treat analysis, but those having protocol deviations in surgical technique will be removed from the per-protocol analysis. The study flow, assessment and analysis can be seen in figure 1.

Patient eligibility

Inclusion criteria

1. All patients suitable for TKA age 40–75 years with a primary diagnosis of OA.
2. Patients who meet the indications for primary unilateral TKA using the Stryker Triathlon cruciate-retaining TKA system.

Exclusion criteria

1. Knee flexion <90° and knee flexion contracture >15° at preoperative assessment.
2. Coronal deformity with hip-knee-ankle (HKA) angle >15° varus and >10° valgus on standing long-leg radiographs.
3. Prior grade 3 injury[55 56] to PCL, posterolateral corner, lateral collateral ligament or medial collateral ligament.
4. TKA requiring increased prosthetic stability (posterior stabilised, constrained condylar or rotating hinge designs), diaphyseal stems or metal augments.
5. TKA for causes other than OA (inflammatory arthritis, post-traumatic arthritis, tumour or acute fracture).
6. Prior contralateral TKA within 6 months of current surgery.
7. Any prior knee surgery apart from arthroscopic surgery or anterior cruciate ligament reconstruction.
8. Prior femoral, tibial or patellofemoral osteotomy.
9. Symptomatic grades 3–4[57] ipsilateral ankle or hip arthritis.
10. The participant unable to attend clinical follow-up for a minimum of 2 years.
11. The participant unable to provide informed consent (due to cognitive capacity or English proficiency).

Allocation

Informed consent from patients meeting eligibility requirements will be obtained by the treating surgeon and consent for the randomisation and patient reported aspect of the study will be obtained electronically via RAPID. Consented participants will be allocated to treatment via a computer-generated randomisation schedule with balanced variable blocks. Stratification will be by surgeon. Patients will be assigned to one of the four treatment groups consisting of assistance grouping (RAS or CAS) and alignment grouping (KA or MA) (table 1). The surgical team will be notified of assistance group allocation ten days prior to surgery to allow for equipment scheduling. However, notification of alignment treatment allocation will occur at induction of anaesthesia.

Treatment arms: cohort rationale and technique

Online supplemental 2 provides a detailed surgical technique for each cohort. Alignment targets are listed in table 2. Surgeons will follow the general principles for each cohort.

Cohort 1: RAS+KA

RAS will be performed using a preoperative CT matched resections protocol with restricted KA boundaries being imposed if required. Virtual intraoperative gap balancing will then be performed with the aim to achieve functional gap balance at 10° and 90°. Any preresection adjustments to the original KA plan in order to achieve balanced gap targets will be recorded. Adjustments must not exceed predetermined restricted safe zone boundaries. Any further bone cuts or soft tissue releases to achieve balance is permitted and will be recorded.

Cohort 2: RAS+MA

RAS will be performed with MA resection angle targets. Only soft tissue balancing is permitted and will be recorded. In order to ensure MA is maintained, no adjustments to prosthetic alignment are permitted.

Cohort 3: CAS+KA

CAS will be performed using a preoperative plain radiographic KA resection plan. Coronal resection angles to achieve matched bone resections will be determined from digital templating of long leg radiographs, with the tibial sagittal resection angle determined using a lateral knee radiograph. As per RAS+KA cohort, restricted alignment boundaries will be imposed if required. Any further bone cuts or soft tissue releases to achieve balance are permitted and will be recorded.

Cohort 4: CAS+MA

CAS will be performed with MA resection angle targets. Soft tissue balancing is permitted and will be recorded. In order to ensure MA is maintained, no adjustments to prosthetic alignment are permitted.

Primary outcome

The primary outcome will be the between-group differences in the mean of the KOOS-12 between preoperative and up to 2 years postoperatively comparing groups within the main interventions:

1. RAS as the surgical assignment intervention compared with CAS as the control.
2. KA as the alignment intervention compared with MA as the control.

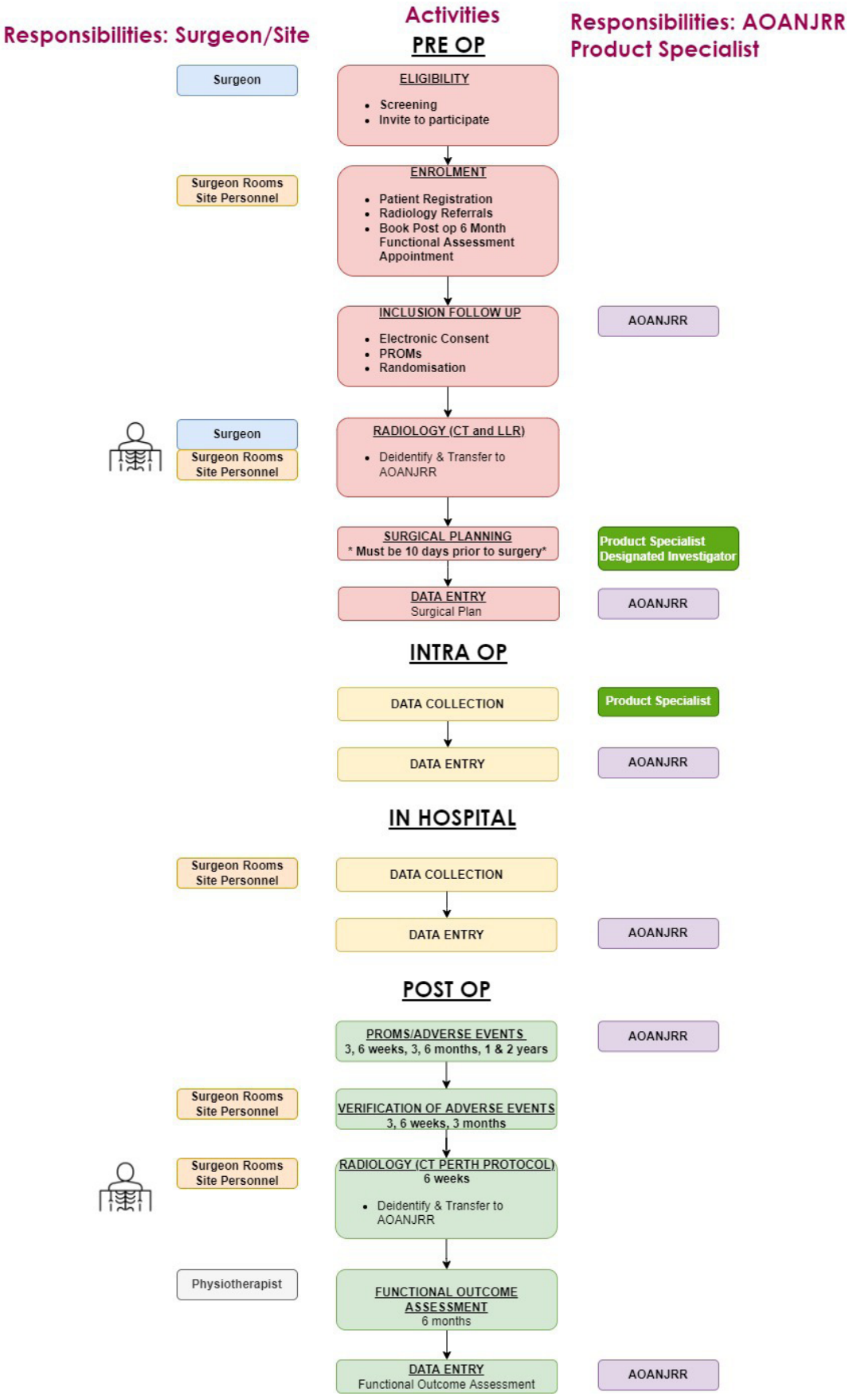

Figure 1 RASKAL study flow diagram. AOANJRR, Australian Orthopaedic Association National Joint Replacement Registry; LLR, Long Leg Radiographs, PROMs, patient-reported outcome measure; RASKAL, Robotic-assisted surgery and kinematic alignment in total knee arthroplasty.

Table 1 2×2 factorial table for patient assignment

		Assistance group	
		Intervention 1 (RAS)	Control 1 (CAS)
Alignment group	Intervention 2 (KA)	*RAS +KA*	*CAS+KA*
	Control 2 (MA)	*RAS +MA*	*CAS+MA*

CAS, computer-assisted surgical; KA, kinematic alignment; MA, mechanical alignment; RAS, robotic-assisted surgical.

Secondary outcomes

Secondary outcomes will be categorised as PROMs, tibiofemoral compartment pressure loads, radiographic outcomes, functional outcome measures, implant survivorship and complications. Table 3 provides a detailed list of all outcome measures, time points and purpose.

Patient-reported outcome measures

Secondary PROMs will include the Oxford Knee Score (OKS)[58] for knee-specific pain and function, the Forgotten Joint Score-12 (FJS-12)[58] as a measure of joint awareness and EuroQoL-5 Dimension-5 Level (EQ-5D-5L)[59 60] for assessment of general health and quality of life. Patient perceived satisfaction, joint symptom change and Visual Analogue Scale (VAS) pain scores[61] will be recorded at multiple time points.[62] Early postoperative recovery will be studied at 3 and 6 weeks using the OKS, VAS pain scores[61] and opioid analgesic requirements.

Tibiofemoral compartmental pressure loads

Compartmental pressure loads will be recorded once final implants have been inserted (Verasense System, OrthoSensor, Dania Beach, Florida, USA) to assess knee balance. 'Balance' will be defined as a pressure difference of ≤15 pounds per square inch (psi) between the medial and lateral compartments at all flexion angles with no individual pressure exceeding 40 psi. Final compartmental pressure loads will be recorded at three knee flexion angles (10°, 45° and 90°). The surgeon will be blinded to the pressures and will not be able to perform knee balancing based on the readings.

Radiographic outcomes

A CT Perth Protocol[63] obtained within 6–8 weeks postoperatively will measure HKA, Lateral Distal Femoral Angle (LDFA) and Medial Proximal Tibial Angle (MPTA) coronal angles, femoral and tibial component sagittal angles, femoral component rotation and femorotibial component match. The alignment difference (AD=absolute final intraoperative navigation alignments minus postoperative CT alignments) will be calculated for each angular variable. The proportion of participants with an AD within and inclusive of ±2° and ±3° will be determined for each angular variable and compared between groups. Routine knee radiographs will be performed postoperatively, 1 and 2 years (AP erect, lateral and skyline view).

Functional outcomes

Functional outcomes will be assessed 6 months postoperatively by a physiotherapist blinded to treatment allocation. Knee range of motion will be measured using a photographic method with the patient in the supine position to allow for repeatability.[64] PCL stability will be graded at 90° of knee flexion.[65] A Timed Up and Go test

Table 2 Alignment boundaries for kinematic alignment and targets for mechanical alignment cohorts

Parameter	Restricted kinematic alignment boundaries	Mechanical alignment targets
HKA angle	6° varus to 3° valgus	0°
Femoral coronal resection angle	6° valgus to 3° varus	0°
Femoral sagittal resection angle	0°–6° flexion	0°–6° flexion
Femoral rotational resection angle	Parallel (0°) to PCA, with boundaries of –6° IR to +6° ER to surgical TEA.	Parallel (0°) to surgical TEA. Secondarily, 3° externally rotated to posterior condylar axis and perpendicular to femoral AP axis.
Tibial coronal resection angle	6° varus to 3° valgus	0°
Tibial sagittal resection angle	0°–6° flexion	0°–6° flexion
Tibial rotational angle	Tibial AP axis	Tibial AP axis

Aim for HKA target to be within ±2° for HKA and ±1° for all other implant targets.
Sagittal alignments (FSRA and TSRA) are patient-specific, with FSRA aimed to optimise component fit, and TSRA aimed to restore native tibial slope.
AP, anteroposterior; CAS, computer-assisted surgical; ER, external rotation; FSRA, Femoral Sagittal Resection Angle; HKA, hip-knee-ankle; IR, internal rotation; KA, kinematic alignment; MA, mechanical alignment; PCA, posterior condylar axis; RAS, robotic-assisted surgical; TEA, surgical transepicondylar axis; TSRA, Tibial Sagittal Resection Angle.

Table 3 List of study outcomes, time schedule and purpose of measures

Outcome	Assessment time points									Purpose
	Pre	0 w	3 w	6 w	3 m	6 m	1 y	2 y	>2 y	
Patient-reported outcome measures										
KOOS-12	x				x	x	x	x		Knee-specific instrument used for primary outcome to assess pain and function after TKA.[52]
OKS	x		x	x	x	x	x	x		Knee-specific instrument used for secondary outcome to pain and function after TKA.[58]
FJS-12	x				x	x	x	x		Knee-specific instrument to measure patients' awareness of their knees in everyday life.[75]
EQ-5D-5L	x									Overall measure of health status.[59 60]
VAS pain	x		x	x	x	x	x	x		Unidimensional measure of pain rated over last 7 days.[61]
Analgesic use		x	x	x						Measures of strong pain medication use (excluding paracetamol & anti-inflammatory agents) over last 7 days.
Patient satisfaction					x	x	x	x		Satisfaction rating of surgery using five option Likert scale from 'very dissatisfied' to 'very satisfied'.[62]
Patient joint change					x	x	x	x		Perceived change rating after surgery using five option Likert scale from 'much worse' to 'much better'.
Intraoperative assessment of balance										
		x								Knee compartment pressures as a measure of soft tissue balance following prosthetic implantation.[76] The surgeon will be blinded.
Radiographicassessment										
CT perth protocol				x						Postoperative CT measurement of implant positioning in coronal, sagittal and axial planes to determine precision of surgical assignment group.[63]
Plain radiograph							x	x		Postoperative X-ray assessment to monitor for implant loosening and subsidence.
Functional assessment										
Knee ROM						x				Standardised photographic measurement to allow repeatability and blinding of knee ROM.[64]
Timed up and go test						x				Measurement of time to stand up from a standard seat, walk three metres, turn, walk back and sit down.[66]
6 min walk test						x				Measurement of maximal walking distance attainable over 6 min along a 25 metre path.[67]
Stair climb test						x				Measurement of time to ascend and descend a flight of 12 steps to help differentiate higher levels knee function.[68]
Single leg stance test						x				Measurement of time capacity to stand on the operated leg as a measure of proprioception, strength and balance.[69]
Complications										

Continued

Table 3 Continued

Outcome	Assessment time points								Purpose
	Pre	0 w	3 w	6 w	3 m	6 m	1 y	2 y	>2 y	
		x	x	x	x					Measurement of surgical and non-surgical adverse events following surgery.
Implant survivorship										
		x	x	x	x	x	x	x	x	Measurement of implant survivorship recorded through standard processes of AOANJRR.

AOANJRR, Australian Orthopaedic Association National Joint Replacement Registry; EQ-5D-5L, EuroQoL-5 Dimension-5 Level; FJS-12, Forgotten Joint Score 12; KOOS, Knee injury and Osteoarthritis Outcome Score; m, months; OKS, Oxford Knee Score; Pre, preoperative; ROM, range of motion; TKA, total knee arthroplasty; VAS, Visual Analogue Scale; w, week; y, years.

will be performed starting from a standard seated position and over a distance of 3 m.[66] A Six Minute Walk Test (6MWT) will also be performed over a 25 m path. The distance the patient is able to ambulate will be measured a trundle wheel. High repeatability of the 6MWT test has been established in patients awaiting TKA.[67] The Stair Climb Test will measure time to ascend a flight of twelve steps. This test has excellent responsiveness and may help differentiate higher levels knee function.[68] A Single Leg Stance Test will measure the longest time participants can stand on the non-operated leg with their eyes open and maintain their balance. The test will then be repeated on the operated leg. The goal is to assess the balance, proprioception and limb strength.[69]

Implant survivorship

Nesting of this study within the AOANJRR allows for the routine monitoring of primary TKA to determine if and when they have been subsequently revised, or the patient is deceased. This information is then used to calculate the time to revision.

Complications

Participants will be monitored for complications and will include serious adverse events, both related and unrelated to the operation (online supplemental 3). Participants will be screened for complications by their surgeon and by study coordinators via telephone consults at multiple time points.

Sample size

KOOS-12 has been demonstrated to have similar responsiveness and validity to the full KOOS.[70] Roos reported a change in KOOS Pain, Symptoms and Function subscales of 45, 37 and 41 (mean 41) in patients undergoing TKA.[52 71] The minimal clinically important change in KOOS is considered to be between 8 and 10, with a SD of 16. A sample size of 192 participants (12 surgeon clusters and 16 patients per surgeon) provides 93% power to detect a 0.5 SD difference (eight points) in the primary outcome (KOOS-12) for each of the comparisons being tested (CAS vs RAS and MA vs KA). The target sample size of 300 (20 patients from each of 15 surgeons) allows for loss of three surgeons and 20% patients lost to follow-up.

Data collection and monitoring

AOANJRR will undertake data collection through the RAPID platform. Preoperative and perioperative data collection will be performed by site and central coordinators. PROMs data will be collected electronically and telephone follow-up for non-responders. Radiographic and functional outcomes will be performed by radiographers and physiotherapists blinded to treatment allocation. Implant survivorship will be monitored by routine AOANJRR processes of identification. The complete schedule of collected study data can be seen in online supplemental 4.

Data analysis

Two statisticians will write a detailed statistical analysis plan. One statistician will oversee participant randomisation and prepare the analytical datasets. The second statistician undertaking the analysis will be blinded to the treatment allocation. If between-group differences exist, agreement on the interpretation will be reached by the writing group and statisticians prior to unblinding of investigators.

The primary analysis will include a generalised linear mixed model for repeated measures for continuous KOOS-12 scores. This approach allows for repeated measures on the same participants at multiple time points (preoperative, 3 months, 6 months, 1 year and 2 years postoperatively). When examining between-group differences for KA and MA for primary and secondary endpoints, the effect of patient preoperative knee phenotype based on constitutional alignment (varus, neutral, valgus) and joint line obliquity (apex distal, neutral, apex proximal) will be considered using the CPAK classification.[30] Patient and knee phenotype will be included as a random effect and an unstructured covariance structure will be specified to account for variability at each measurement time. RAS, KA, along with measurement time and their interaction(s) will be included as fixed effects in the model. Both unadjusted and adjusted analyses for measured confounders will be undertaken. Effect sizes will be estimated with 95% confidence limits and statistical significance will be assessed at the 5% level.

We will use the OMERACT-OARSI criteria to measure positive 'responder status'[72] between groups using the following criteria:

1. Relative improvement in KOOS-12 pain or KOOS-12 function of ≥50% and absolute change ≥20%.
2. At least two out of three of the following: (1) relative KOOS-12 pain improvement ≥20% and absolute change ≥10%; (2) relative KOOS-12 function improvement ≥20% and absolute function change ≥10% and (3) joint change rated as ' much better'.

The proportion of participants in each group reaching Patient Acceptable Symptom State thresholds will be examined for KOOS-12 (threshold 84) and OKS (threshold 37) based on prior analyses.[73 74] The influence of CPAK phenotype will be on between-group differences will be examined using KOOS-12, OKS and FJS-12.

AOANJRR describes the time to first revision using the Kaplan-Meier estimates of survivorship. The cumulative percent revision accounts for right censoring due to death or closure of the database at the time of analysis. The unadjusted cumulative percent revision with an accompanying 95% CI will be calculated with the use of unadjusted pointwise Greenwood estimates. Hazard ratios will be calculated using Cox proportional hazards models adjusting for confounders and will be used to compare the rate of revision between the KA group, the RAS group and if there is an interaction between KA and RAS. The assumption of proportional hazards will be checked analytically for each model.

If a significant and clinically important between-group difference is found comparing RAS and CAS TKA, a cost-effectiveness analysis will be performed from a health service perspective to determine the cost per unit health gain on the KOOS-12 scale and using the EQ-5D-5L to determine cost per quality-adjusted life-year gain.

Patient and public involvement

Neither patients nor the public were involved in the development of the research question, study design or implementation of this trial.

Ethics and dissemination

Ethics approval has been obtained through a central Human Research Ethics Committee (Sydney Local Health District- Royal Prince Alfred Hospital), Approval X20-0494 and 2020/ETH02896 10.24/DEC20) as well as individual site approvals. Any significant modification to the protocol will be submitted to ethics committee and individual sites for approval.

The results of this research will be presented at national and international orthopaedic meetings. We aim to have this research submitted to a high impact, peer-reviewed journal for publication.

Safety considerations

The interventions of RAS, CAS, MA and KA are currently undertaken as routine surgical practice. We do not anticipate that either intervention or control arms will be associated with any adverse events beyond those that patients are normally exposed to during TKA. We have also defined a KA protocol with restricted alignment boundaries that we believe will not expose patients to risk in terms of prosthetic complications from alignment deviations that unintentionally occur with conventional instrumentation. As both RAS and CAS have shown high levels of precision in the literature,[15 17 18 21 22 26 28 29] we believe the risk of malalignment is low when compared with conventional instruments which remains the most common method of prosthetic implantation.

Investigators and study coordinators will report any adverse events to the trial coordinators without undue delay. Complications determined to be a serious adverse device effect (SADE), unanticipated SADE or significant safety issue will be reported following research guidelines. Notification of all deaths to the HREC will occur biannually following the matching of Registry core data to the National Death Index.

Stopping rules

This trial will not involve a primary safety endpoint as the devices and technologies involved are already entered onto the Australian Register of Therapeutic Goods and are in common use. The risks of participating in the study will be comparable to standard medical care. The technology and alignment strategies will be used in accordance with its intended use and in a manner already used both nationally and internationally. For these reasons, formally written stopping rules for harm are considered

unnecessary for this study. Furthermore, because recruitment will finish prior to the collection of the primary endpoint, it is anticipated that there will not be a need for stopping rules based on the primary outcome.

Data management

Data will be collected and stored in the AOANJRR database within South Australian Health and Medical Research Institute (SAHMRI) which is protected by the Quality Assurance Activity legislation of the Health Insurance Act of 1973. SAHMRI will provide information technology, data management and statistical analysis services.

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