Robotic-assisted surgery and kinematic alignment in total knee arthroplasty (RASKAL study). A registry-nested, multi-centre, 2 x 2 factorial randomised trial of clinical, functional, radiographic and survivorship outcomes.

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1   Introduction

Total knee arthroplasty (TKA) is a successful operation for the majority of patients with end-stage arthritis in terms of reducing pain and improving function [1]. However, up to 18% of patients report some dissatisfaction following TKA [2-4] with the most common reason for surgery being persistent knee pain [3-9]. Pain may result from inappropriate soft tissue balance resulting in stiffness, instability, asymmetric joint laxity and patellofemoral maltracking [10-15].

In an attempt to improve patient outcomes, two significant surgical developments with independent aims have occurred within the last decade. Firstly, robotic-assisted surgery (RAS) has rapidly been adopted with the aim of increasing the alignment precision, soft tissue balance and reducing soft tissue trauma in TKA [16-19]. Secondly, kinematic alignment (KA) techniques which aim to restore the patient's constitutional anatomy and soft tissue laxities [20-27] have been introduced [28-32]. Adoption of both continues to increase with 21% of American Association of Hip and Knee Surgeons surveyed in 2018 using robotic-assisted techniques in their practice and 10% using KA or other alternative alignment strategies [33].

1.1   Robotic-assisted surgery in TKA

Computer-assisted surgical (CAS) navigation remains the gold standard alignment method in TKA. When compared to RAS-TKA, there are few high-quality comparative studies [34] and most with first generation robots which are no longer in use. Meta-analyses have confirmed the precision of CAS with 12.8% of mechanically aligned TKAs being deviated more than 3 degrees from a neutral HKA angle versus 30.1% with conventional instruments [35, 36]. More recently, the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) reported a reduced rate of revision in patients less than 65 years of age who had a TKA aligned by CAS when compared to conventional techniques [37].

Until recently, RAS in TKA has not been widely adopted because of increased costs, operating time, surgical complexity and contradicting outcome data supporting its use [38-43]. Recent refinements in robotic-assisted cutting instruments has increased adoption [33], particularly with the use of the MAKO (Stryker, Kalamazoo, MI, USA), Navio (Smith and Nephew, Memphis, TN, USA), and ROSA (Zimmer Biomet, Warsaw, IN, USA) systems . The software platforms of most RAS systems provide virtual gap-balancing algorithms that allow adjustments in angular bone resections prior to definitive bone resections being made to potentially improve knee balance [44]. Further, the MAKO robotic-assisted cutting arm has a unique haptic system that prevents the saw blade from advancing beyond

the programmed field of bone resection. This may reduce intra-operative soft tissue trauma and potentially enhance early recovery [45, 46]. Early efficacy, relatively short learning curves and safety with latest generation robotic arm technology has been demonstrated but high-quality comparative studies, particularly compared to CAS have not been performed [47-52].

1.2 Alignment in TKA

The standard technique in TKA is the mechanical alignment (MA) method which aligns implants perpendicular to the femoral and tibial mechanical axes with compensatory external rotation of the femoral component to adjust for a neutral tibial resection [28]. Bellemans et al, however, found that for normal subjects, the mechanical axis of the lower limb is in slight varus with one third of males having more than 3 degrees of constitutional varus. Lastly, the joint line obliquity is not perpendicular to the lower limb mechanical axis, but angles distally and medially, resulting from 2.1 degrees of mean distal femoral valgus and 3 degrees of mean proximal tibial varus [53].

Recently, KA-TKA has evolved with the aim of restoring native knee alignment to improve knee balance and patient outcomes [24, 25, 54, 55]. In its purest form, KA positions the implant on the bone surface to prioritise soft tissue balance, without restrictions on final implant position. However, placing implants in extreme positions may predispose to subsidence, loosening and ultimately TKA failure. For this reason, surgeons may decide to implement alignment boundaries to reduce potential risks of malposition. Unfortunately, this leads to ambiguity in the literature with multiple methodologies and descriptions being used under the umbrella term "kinematic alignment".

To date, studies have compared KA using patient-specific cutting guides to other methods including CAS and conventional guides [20, 21, 23, 56] which all have varying degrees of accuracy [36, 37, 57]. This variability may detract from the potential benefits of KA. A meta-analysis of randomised trials found no statistically significant difference in patient-reported outcome measures (PROMs) in the KA patients, with long term outcomes remaining unknown [58]. Lastly, a concern regarding KA techniques is the variability in alignments that may predispose to implant failure, especially when using techniques with lower degrees of precision. A retrospective, registry-based study found similar revision rates at seven years between kinematic and non-kinematic implant positioning [59]. A single surgeon series of 157 KA-TKAs at 10 years showed an all cause survival of 97.4% and aseptic survival of 98.4% [60].

More recently, the term functional alignment (FA) has been introduced [61] which is a hybrid of

both KA and MA. FA aims to provide a balanced knee whilst keeping the limb alignment within safe limits. To maintain consistency with descriptions used in prior studies, KA will be used to describe this alternative individualised alignment strategy, although by its strictest definition, the technique used in this study will more closely replicate "restricted KA", and in cases where gap balancing is additionally performed, "functional alignment".

2   Justification for a new trial

Given the significant expenditure invested in RAS-TKA, along with increasing adoption of KA-TKA, analysis of patient outcomes and implant survivorship is required compared to the current gold standards of surgical care. To the best of our knowledge, no appropriately designed randomised trials have been undertaken to answer these important questions. In addition, no studies have assessed whether improved outcomes from RAS-TKA occur from increased surgical precision due to refinements in cutting technology, the reduction in soft tissue trauma enabled by haptic boundaries, the restoration of knee balance related to KA with virtual gap balance or a combination of these factors. It is critical that any study separates out these independent surgical variables to determine the efficacy of each surgical process whilst examining interactions that may occur between each.

3   Aims

The purpose of this research is to assess the capacity of RAS-TKA, KA or both to improve clinical outcomes, functional measures, radiographic precision and prosthetic survivorship when compared to the current gold standards of surgical care using the Triathlon Total Knee System and MAKO Robotic Platform (Stryker, Kalamazoo, MI, USA).

The primary aims are:

1. To determine if there is a difference between RAS-TKA and CAS-TKA, as measured by changes in Knee Injury and Osteoarthritis Outcome Score 12 (KOOS-12) over two years.
2. To determine if there is a difference between KA-TKA and MA-TKA, as measured by changes in KOOS-12 over two years.

Secondary aims include assessing how RAS and KA affect other PROMs, radiographic alignment and implant survival. Interaction between the two treatment types will be explored. Long term follow-up using implant survival from routine registry data will also be reported.

4   Methods and analysis

4.1   Study Design

We will conduct a registry-nested, multi-centre, 2x2 factorial, randomised trial. A factorial study offers an efficient method of analysing the two different surgical processes independently whilst examining the interactions that may occur between instruments to align the knee, method of alignment and method of balance. In addition, a factorial study increases power of the study, minimising unnecessary participant exposure to interventions being assessed [62]. The study will be nested within the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) utilising the RAPID (Real time Automated Platform for Integrated Data capture) system [63]. The study protocol was reviewed and endorsed by the executive committees of the Australian Society of Arthroplasty (ASA) and Australian Knee Society (AKS).

Patients undergoing TKA will be randomly allocated to an assistance group (RAS or CAS) and an alignment group (KA or MA), following a 2x2 factorial design (See Table 1). Patients will be assigned as follows:

1.   robotic-assisted TKA with kinematic knee alignment (RAS-KA group)

2.   robotic-assisted TKA with mechanical knee alignment (RAS-MA group)

3.   computer-assisted TKA with kinematic knee alignment (CAS-KA group)

4.   computer-assisted TKA with mechanical knee alignment (CAS-MA group)

Table 1. 2 x 2 Factorial table for patient assignment

		Assistance Group	
		Intervention 1 (RAS)	Control 1 (CAS)
Alignment	Intervention 2 (KA)	*RAS - KA*	*CAS - KA*
Group	Control 2 (MA)	*RAS - MA*	*CAS - MA*

Each participating surgeon must have undergone formal MAKO RAS training and have performed a minimum of 10 RAS-TKA and 10 CAS-TKAs with kinematic alignment to mitigate any learning curve effect [50, 64]. Surgeons will not be blinded because of the requirement to undertake the intervention. Participants, non-surgical investigators and statisticians performing the analysis will be blinded to the interventions received.

4.2 Study Locations

Fifteen surgeons from 10 hospitals across Australia met the participation criteria and agreed to be a part of the surgeon workgroup. Each surgeon signed an agreement letter to be a 'surgeon investigator' for the RASKAL Study and that they met the above specifications. The surgeon workgroup met over a 6-month period to refine the study protocol and surgical technique guide to ensure that a pragmatic, patient-centred trial was undertaken.

4.3 Study Group

Potential patients will be screened for eligibility by the individual surgeon and their orthopaedic team. Patients who meet the eligibility criteria will be invited to participate and will be given an information sheet to educate them on the purpose of the trial, its blinded nature, and requirements for participation.

5 Patient Criteria

5.1 Inclusion criteria

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

5.2 Exclusion criteria

1. Knee flexion < 90 degrees and knee flexion contracture > 15 degrees at preoperative assessment
2. Coronal deformity with hip-knee-ankle (HKA) angle > 15 degrees varus and > 10 degrees valgus on standing long-leg radiographs
3. Prior grade 3 injury [65, 66] to posterior cruciate ligament, 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 osteoarthritis (inflammatory arthritis, post-traumatic arthritis, tumour or acute fracture)
6. Prior contralateral TKA within 6 months of current TKA surgery
7. Any prior knee surgery apart from arthroscopic surgery or anterior cruciate ligament reconstruction
8. Prior femoral, tibial or patellofemoral osteotomies
9. Symptomatic grade 3-4 [67] ipsilateral ankle or hip arthritis

10. The participant unable to attend clinical follow-up for a minimum of 2 years

11. The participant is unable to provide informed consent (due to cognitive capacity or English proficiency)

6 Allocation

Allocation to treatment via randomisation (1:1:1:1) will occur at the time of patient consent for study inclusion. This will allow for surgical planning for RAS-TKA however, only patients assigned to RAS-TKA will have formal MAKO planning for surgical execution. A member of the study team will contact the AOANJRR project team by telephone at the time of patient consent to initiate surgical planning. Only the study team will be aware of the allocation at this stage. Robotic engineers will be notified ten days prior to the surgical date for segmentation and planning. The surgical team will be advised of the allocation to RAS or CAS ten days prior to surgery to allow for scheduling of equipment. Attempts will be made by the surgical team to maintain patient blinding during this time. KA or MA allocation will occur at the induction of anaesthesia and the surgeon will remain blinded until the procedure. Stratification will be by surgeon. Allocation of the treatments will follow a computer-generated randomisation schedule with balanced variable blocks.

7 Preoperative investigations and planning

All participants will undergo preoperative surgical planning with a computed tomographic (CT) scan and standing long leg radiographs (LLR) of the lower limb. A blinded study radiographer will analyse all CT scans and LLR's for preoperative measurements. The HKA angle, lateral distal femoral angle (LDFA), medial proximal tibial angle (MPTA), sagittal femoral angle (SFA), sagittal tibial angle (STA) and posterior condylar axis angle (PCA) relative to the surgical transepicondylar axis (TEA) will be measured from the CT scans and LLR's [53]. As CAS-TKA is considered an image-free technique, surgical planning will be based only on LLRs and not CT-based imaging. KA planning will utilise Coronal Plane Alignment of the Knee (CPAK) algorithms to determine femoral and tibial coronal resection angles within the defined restricted safe zone. The KA plans will be constructed by a blinded radiographer and orthopaedic surgeon who is a member of the study group but not the surgical group. Patients allocated to the RAS-KA group will have their KA plan based on preoperative CT imaging as per the MAKO system surgical method. CT imaging of patients undergoing RAS-TKA will also be segmented and analysed by a trained MAKO Product Specialist (MPS) which is a standard

practice for procedures utilising this technique.

In the MA group, the femoral coronal resection angle (FCRA) and the tibial coronal resection angles (TCRA) will be perpendicular (zero degrees) to the mechanical axis of each bone segment with a resultant zero HKA angle. The femoral sagittal resection angle (FSRA) will be set within the range of 0°-6° of flexion. The tibial sagittal resection angle will be set at 3° of flexion. Femoral component rotation will be parallel to the surgical TEA, and secondarily perpendicular to the AP femoral axis and 3° externally rotated to the posterior femoral condylar axis. Tibial component rotation will again be set parallel to the tibial anteroposterior (AP) axis (Akagi's line, referenced from centre of posterior cruciate ligament (PCL) footprint to medial edge of patellar tendon) [68, 69].

In the KA group, the aim is to replicate the constitutional joint line alignment by restoring coronal, sagittal and rotational positioning with a restricted safe zone boundary. The following restrictive safe zones will be set for the KA plan:

1. The FCRA will aim to restore the LDFA within and inclusive of an 84° to 93° boundary (3° varus to 6° valgus).

2. The TCRA will aim to restore the MPTA within and inclusive of an 84° to 93° boundary (6° varus to 3° valgus).

3. If the combined sum of the FCRA and TCRA result in a final HKA outside of 6° varus to 3° valgus, then both the FCRA and TCRA will be incrementally adjusted.

4. The FSRA and the TSRA restrictive safe zones will be from 0°-6° for each. Initial FSRA and TSRA will be determined based off the CT in the RAS-KA cohort and based off the LLR in the CAS-KA cohort. The combined restrictive boundary for sagittal implant positioning (FSRA plus TSRA) will no more than 10°.

5. Femoral component rotation will be set parallel to the posterior femoral condylar axis, referenced off subchondral bone for RAS-KA and the cartilage surface for CAS-KA. Any difference between the native MPTA and planned TCRA will require compensatory external rotation adjustment of the femoral component to accommodate for the angular difference. The restrictive safe zone for femoral component rotation with be inclusive of and within 6° of external rotation to 6° of internal rotation relative to the surgical TEA.

6. Tibial rotation will be set parallel to the tibial AP axis [68, 69].

8   Surgical Technique

All patients will receive a fully cemented, cruciate-retaining prosthesis with patellar resurfacing using the Triathlon Total Knee System. A medial parapatellar approach to the knee will be used in all cases. If the PCL is deemed to be lax or incompetent, then a cruciate-stabilised (CS; anterior-lipped) or posterior-stabilised insert will be utilised. All patients will be included in the primary intention-to-treat analysis, but those having surgical protocol deviations in surgical technique will be removed from the per-protocol analysis. Partial PCL lengthening is allowed for flexion tightness. All patellar implants will be a cemented, oval, onlay design.

The surgical technique for RAS-TKA and CAS-TKA are provided in Appendix 1. Optical navigation will be used until final implantation of prostheses to ensure that target alignments are reached within a range of 1° for final individual component alignment and 2° for final HKA. All surgeries will have coronal, sagittal and rotational alignments recorded at the following time points:

1. once bone resections have been performed (resection validation)
2. after definitive prosthetic implantation

Once definitive femoral and tibial components have been cemented and final polyethylene liner thickness has been determined, an intraoperative pressure sensor (Verasense System, OrthoSensor, Dania Beach, Florida, USA) will be inserted. The surgeon will be blinded to the pressure sensor results. The surgeon will place the same size sensor as the planned definitive polyethylene liner. The knee will be placed in three positions (10°, 45° and 90° of knee flexion) and the medial and lateral compartmental pressures will be recorded. This will be performed twice and the mean pressure in each compartment will calculated. If compartmental pressures overload the sensor, the surgeon will be asked to reset the sensor and repeat the test.

9   Surgical Interventions

9.1   RAS-KA Group

RAS-TKA will be performed with the preoperative programming per the KA plan. Virtual intra-operative gap balancing will then be performed with the aim to achieve symmetrical gap balance. Any adjustments to the original KA plan in order to achieve balanced gaps will be recorded. Adjustments must not exceed the restricted safe zone boundaries. Any further bone cuts or soft tissue releases to achieve balance is permitted and will be recorded.

9.2 RAS-MA Group

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

9.3 CAS-KA Group

The surgeon will perform the CAS-TKA using the Stryker Precision 3 Navigation System with resection angles based on the KA plan. Any further bone cuts or soft tissue releases to achieve balance is permitted and will be recorded.

9.4 CAS-MA Group

CAS-TKA will be performed with MA resection angles using the Stryker Precision 3 Navigation System. Soft tissue balancing is permitted and will be recorded. In order to ensure MA is maintained, no adjustments to alignment are permitted.

10 Postoperative Management

There will be no prescriptive methods of care for pain management, wound management, thromboembolic prophylaxis, in-patient or out-patient rehabilitation, or any other element of postoperative care. As each study surgeon will be contributing an equal number of patients to each factorial group, patients will be managed as per each surgeons' normal preferences and each patients' individual needs without concern for confounding. This will allow for a pragmatic approach to potentially complex postoperative management differences and also allows for patient-oriented treatment to be delivered. Furthermore, it will not interfere with patient driven ideals (e.g. in-patient rehabilitation is superior to out-patient rehabilitation) and therefore not unnecessarily detract from patient's perception of their TKA experience or general satisfaction scores.

11 Outcomes

11.1 Primary Outcomes

The two primary outcomes will be the between-group differences in the mean of the Knee Injury and Osteoarthritis Outcome Scores (KOOS-12)[70] between preoperative and up to 2 years postoperatively comparing groups within the main interventions:

1. RAS-TKA as the surgical assignment intervention compared to CAS-TKA as the control, and
2. KA-TKA as the alignment intervention compared to MA-TKA as the control.

11.2 Secondary Outcomes

11.2.1 Patient-reported outcome measures

The following instruments will be administered to measure changes in between-group differences from preoperative and up to 2 years postoperatively.

1. Knee Injury and Osteoarthritis Outcome Scores (KOOS-12) subscales of Pain, Symptoms and Function measured at 3 months, 6 months, 1 and 2 years postoperatively [70].

2. Visual Analogue Scale (VAS) Pain Score: measured at 3 weeks, 6 weeks, 3 months, 6 months, 1 and 2 years postoperatively. VAS is a unidimensional measure of pain intensity measured from 0 (no pain) to 10 (worst imaginable pain). Patients will be asked to rate the pain they have had in their knee over the last 7 days. This is the method currently used by the AOANJRR PROMs Pilot Project [71].

3. Oxford Knee Score (OKS): measured at 3 weeks, 6 weeks, 3 months, 6 months, 1 and 2 years postoperatively. OKS is a 12-item tool designed to assess pain and function after TKA [72].

4. Analgesic Requirements: measured 3 weeks, 6 weeks and 3 months postoperatively to compare the use of analgesia between groups. Patients will be asked if they used any strong pain medications (excluding paracetamol or anti-inflammatory medications) specifically used for their knee in the last 7 days.

5. Forgotten Joint Score 12 (FJS-12): measured at 3 months, 6 months, 1 and 2 years postoperatively. The FJS-12 focuses on patients' awareness of their knees in everyday life. Low ceiling effects and good relative validity allow monitoring of longer-term outcomes, particularly in well-performing groups after TKA [73].

6. EQ-5D-5L (EuroQoL): measured at 3 months, 6 months, 1 and 2 years postoperatively. EQ-5D-5L is a standard measure of overall health status that provides a simple descriptive profile and an index value for health status [74, 75].

7. Patient-rated Satisfaction and Improvement: this will consist of a 5 option Likert scale from 'very dissatisfied' to 'very satisfied'. It will be measured at 3 months, 6 months, 1 and 2 years postoperatively [63].

8. Joint Change Question: The perceived change in the patients knee after surgery will be assessed using a 5 option Likert scale from 'much worse' to 'much better'. It will be measured at 3 months, 6 months, 1 and 2 years postoperatively.

9. Patient Expectations: Patients expectations in 6 months' time will be assessed by asking questions related to pain, mobility and health status preoperatively.

10. Responder status. The proportion of "responders" between groups will be compared using OMERACT-OARSI criteria and will be measured at 3 months, 6 months, 1 and 2 years postoperatively [76]. Responder status is defined as positive using the following criteria:

> 1. relative improvement in KOOS-pain or KOOS-function of ≥ 50% and absolute change ≥ 20%, or
>
> 2. at least 2 out of 3 of the following:
>
> > i. relative KOOS-pain improvement ≥ 20% and absolute change ≥ 10%
> >
> > ii. relative KOOS-function improvement ≥ 20% and absolute function change ≥ 10%
> >
> > iii. joint change rated as "much better"

11. Patient Acceptable Symptom State (PASS). PASS is defined as an outcomes score threshold for the postoperative score above which a patient considers themselves to have a satisfactory outcome. The proportion of participants in each group reaching PASS will be compared for KOOS-12 and OKS and will be measured at 3 months, 6 months, 1 and 2 years postoperatively. The PASS will be set at 84 for KOOS-12 and 37 for the OKS based on prior published thresholds [76, 77].

11.2.2 Tibiofemoral Compartmental Pressure Loads

Compartmental pressure loads will be recorded to validate whether knee balance has been achieved for each group. A study site coordinator will record compartmental pressures using the Verasense pressure insert during each procedure. Final medial and lateral compartmental pressure loads will be recorded at three knee flexion angles. The sensor examination will be repeated twice at each knee to better gauge mean compartment pressure load once the definitive implant has been cemented. The surgeon will be blinded to the results and hence will not be able to make changes to the soft tissue envelope based on the readings. Knee 'balance' will defined as a pressure difference of less than 15 pounds per square inch (PSI) between the medial and lateral compartments at all flexion angles, an absolute compartmental pressure of less or equal to 40 PSI on any one measurement [78].

11.2.3 Radiographic outcomes

A CT Perth Protocol [79] obtained within 6-8 weeks postoperatively will measure HKA, LDFA, MPTA, femoral and tibial component flexion, 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 degrees will be determined for each angular variable and compared between groups. A routine series of radiographs will also be performed postoperatively, 1 and 2 years (AP erect, lateral and skyline view).

11.2.4 Functional Outcome Measures at 6 months

A trained, blinded research physiotherapist for each site will record:

1. Knee range of motion – Photographic measurements will be performed in supine position [80] which allows repeatability and blinding. The following will be recorded; maximal active extension (hyperextension being negative, full extension as zero and flexion contracture as positive); maximal active flexion; and arc of knee motion (flexion minus extension).

2. Timed Up and Go (TUG) Test – Participants will be asked to stand up from a standard seat (height 44-47cm), walk a distance of 3 meters (marked on the floor) at a comfortable pace, turn, walk back and sit down. Participants will be permitted to use routine walking aids and will be instructed not to use their arms to stand up. This task will be performed twice. Shorter times indicate better performance [81].

3. Six Minute Walk Test (6MWT) – Participants will be instructed to walk as far as possible for six minutes up and down a 25-metre path. If they are unable to complete six minutes, they will be instructed to maintain their position whilst the assessor measures the final partial lap with a trundle wheel. The use of a walking aid and standing rests will be permitted. High repeatability of the 6MWT test has been established in patients awaiting TKA [82].

4. Stair Climb Test (SCT) – Participants will be instructed to ascend and descend a flight of 12 steps (no greater than 18cm in height) as quickly as they can while still feeling safe and comfortable. The use of a handrail is allowed if required although participants will be encouraged to use only their legs. Furthermore, an assistive device is allowed if required to complete the test. This test has excellent responsiveness (more so than the 6MWT) and may help differentiate higher levels knee function[83].

5. Single Leg Stance Test (SLST) – Participants will be asked to stand on the unaffected leg with their eyes open and maintain their balance for as long as possible. They will then repeat the test on the operated leg. Three attempts will be made with the best score being used for the final result. The goal is to assess the balance, proprioception and limb strength. This test is a

component of the Delaware Osteoarthritis Physical Assessment (DOPA) protocol [84]

11.2.5 Implant Survivorship

Each hospital will provide operative data on specific Registry forms. These are completed in theatre at the time of surgery and submitted to the Registry each month to be entered into the Registry database. The Registry will determine if any primary procedure has been subsequently revised by matching procedure records by the patient details provided. This information is then used to calculate the time to revision.

12 Data Collection

12.1 Patient Characteristics and Peri-operative Data

1. Baseline Measures

    Baseline demographics will include age at time of surgery, site, gender, side of surgery, height, weight, American Society of Anesthesiologists (ASA) physical classification grading [85] and preoperative active range of motion.

2. Operative Data

    Operative data to be recorded will include:

- size of femoral component, size of tibial component, insert stability (CR, CS, PS), thickness of tibial bearing, size of patellar implant
- total operating time from wound incision to skin closure
- initial and final alignments recorded for HKA, FCRA, TCRA, FSRA, TSRA, and FCRA
- soft tissue releases; medial structures, lateral structures, PCL lengthening, lateral patellar retinacular to achieve balance
- bone alignment re-adjustments to achieve balance
- any operative complications

12.2 In-Hospital Data

In-hospital data will include:

- total length of stay (in hours)
- time to "readiness for discharge" (defined as a patient who is mobilising independently, has pain controlled by oral analgesics and is independent with self-care)
- discharge destination (home, in-patient rehabilitation unit, residential aged-care facility)
- blood transfusion requirements (total number of units administered)
- in-hospital complications (Appendix 2)

The schedule of study assessments and follow-ups can be seen in Appendix 3.

12.3 Data collection approach

The AOANJRR will undertake data collection through the RAPID Platform. Preoperative and perioperative (in-hospital) data collection will be performed by site coordinators via the RAPID platform. Patient PROMs data collection (pre and post-surgery) will be performed online and then followed up by telephone in non-responders. Post-operative reminders will be triggered by the RAPID system once the procedure form has been received by the Registry and a procedure date has been recorded. Reminders will be sent to the patient to complete their pre and post-op PROMs data via RAPID. The type of follow-up that will occur depends on the contact details provided by the participant. The ideal follow up method sequence will be

- Email
- SMS to mobile phone
- Follow-up phone call conducted centrally by the Registry

A maximum of three successful reminders will be sent to the patient, this includes both automated reminders (email and SMS) as well as phone follow up.

Blinded research physiotherapists will be recruited at each centre to undertake functional assessments. A blinded radiographer will perform all preoperative and postoperative radiographic measurements.

13 Statistical Analysis

13.1 Cost-effectiveness analysis

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 (QALY) gain.

13.2 Sample size

The KOOS-12 score has been demonstrated to have similar responsiveness and validity to the full KOOS [86]. Roos et al. in 2003 reported a change in KOOS Pain, Symptoms and Function subscales of 45, 37 and 41 (mean 41) in patients undergoing TKA [70, 87]. The minimal clinically important change in KOOS was considered to be between 8 and 10, with a standard deviation (SD) of 16. A sample size of 192 participants (12 surgeon clusters and 16 patients per surgeon) provides 93% power to detect a 0.5SD difference (8 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.

13.3 Data analysis

Two statisticians will be involved in this study. Together they will write a detailed statistical analysis plan (SAP). One statistician will oversee randomisation of patients to the treatments and prepare the analytical datasets. The second statistician undertaking the analysis will be blinded to the treatment allocation. Following this, if between-group differences exist, agreement on the interpretation will be reached prior to unblinding the 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). Patient will be included as a random effect and an unstructured covariance structure will be specified to account for variability at each measurement time. Robotic assistance, kinematic alignment, 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.

The Registry describes the time to first revision using the Kaplan-Meier estimates of survivorship. The cumulative percent revision at a certain time is the complement (in probability) of the Kaplan-Meier

survivorship function at that time, multiplied by 100. 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% confidence interval (CI) will be calculated with 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 kinematic alignment group, the robotic assistance group and if there is an interaction between kinematic alignment and robotic assistance. The assumption of proportional hazards will be checked analytically for each model.

14 Safety assessment

14.1 Assessment of Complications

Complications to be recorded will include serious adverse events, both related and unrelated to the operation (Appendix 4). Participants will be screened for complications by their surgeon at all postoperative follow-ups and by study coordinators during scheduled telephone consults (Appendix 5). Positive complications reported by patients during 3-month post-operative follow up will be verified by their treating surgeon. The AOANJRR have established an AE Review Committee (AERC) which includes the Clinical Directors and Project Manager. The AERC meet weekly to review each AE in order to evaluate the severity and causality applying a classification to each AE prior to reporting these to the HREC, Site PI, sponsor and AOA Data Safety Monitoring Committee (DSMC). The primary aim of the DSMC is to independently oversee the safety of either industry or surgeon-initiated AOANJRR clinical trials that include the collection of patient and/or hospital reported adverse events (AE). It is proposed the DSMC shall meet at least twice a year or as required. The objective of the DSMC is to:

- be responsible for safeguarding the interests of trial participants
- assess Serious Adverse Event and any Significant Safety Issues
- provide recommendations about stopping, continuing, and modifying the trial based on the need to maximise participant safety.

14.2 Safety considerations

As both 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 surgery. We have also defined a KA protocol with restrictive safe zone boundaries that we believe will not expose patients to risk in terms of prosthetic complications from alignment deviations that can unintentionally occur with conventional instrumentation. As both RAS and CAS have shown high levels of precision in the literature [34-36, 38, 40, 41, 47, 51, 81], we believe the risk of malalignment is low when compared to conventional instruments which remains the most common method of prosthetic implantation.

All trial sites will maintain their own liability and indemnity insurance related to performing this study. There will be additional information in the patient information sheet to allow patients to notify the principal investigators of any adverse events or complications that may arise.

14.3 Monitoring and reporting of adverse events

Principal Investigators will report any adverse events or complications found, detected or brought to their attention, to the AOANJRR without undue delay. All reported complications will be classified (see appendix 6) and reported according to the NHMRC Guidelines (see Appendix 7). Complications determined to be a Serious Adverse Device Effect (SADE), Unanticipated Serious Adverse Device Effect (USADE) or Significant Safety Issue (SSI) 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 NDI. NDI matching provides 'fact of death" data only and no causality is determined.

If patients contact the AOANJRR, they are informed to contact their operating surgeon. If the complication is considered a SAE, AOANJRR will inform the patient that this will be reported to their surgeon for safety monitoring purposes and will request that the patient also contact their surgeon.

15 Ethics

The AOANJRR Project team will obtain ethics approval as well as local site approvals. All ethics and site approvals will be obtained prior to commencing patient recruitment at participating sites. Ethics approval may be obtained through an institutional Human Research Ethics Committee (HREC) or through a central HREC if the site accepts approvals through National Mutual Acceptance. The trial will be registered with the Australian New Zealand Clinical Trials Registry. Each site will also be separately registered under the ethics submission. The investigators believe that conducting this randomised trial to determine if there is any benefit of using RAS-TKA and kinematic alignment, as the potential benefits of this study to society will outweigh any potential risks to participants. As all groups are receiving accepted standards of care for knee surgery, we see no significant risks to the patient that will be outside the normal treatment and care for those patients undergoing TKA. None of the participants in this study will be paid.

16 Consent

Patients determined by their surgeon as eligible will be informed of the study and invited to participate. Surgeons will then proceed with the standard consent for the surgery as per their local hospital process. Informed consent will be obtained at a minimum of 10 days prior to surgery in order to ensure the radiographic investigations are completed preoperatively.

Patients will consent to the randomisation of the surgical technique and to participate in the patient reported aspect of the registry-nested study. This will be obtained electronically via RAPID. The participant information and consent form will be displayed on the screen. It contains all elements typically required for a consent form. The information under each statement will be expandable. Patients will be provided the option to 'learn more' and expand the information if they wish. If the patient chooses to learn more the additional information will be displayed. Once all statements have been reviewed by the patient, they will be able to choose whether they give consent or no longer wish to participate in the study. If the patient consents to participate they will be directed to the next page where they can complete the required pre-operative PROMs instruments. Culturally and linguistically diverse (CALD) participants can nominate a family member, friend or associated support group to assist them to comprehend the Patient Information Sheet (PIS) and consent online.

If the patient chooses not to consent after the initial registration, then all personal information collected at registration will be deleted from the database.

The only data that will be retained is:

- site name
- surgeon name
- date of registration

16.1 Waiver of Consent

We are requesting waiver of consent for the 'registration' process in the RAPID system.

16.1.1 Waiver of consent: Patient Registration

The AOANJRR is requesting a waiver of consent to register patients in the system prior to collecting informed consent. The surgeon investigators and research officers will provide the patient with a hard copy PIS and asked verbally to be registered online for the study. The data that will be stored within the AOANJRR between registration and consent includes:

•   Patient First Name

•   Patient Middle Name

•   Patient Surname

•   Date of Birth

•   Postcode

•   Hospital

•   Surgeon name

•   The joint that will be operated on (Hip, Knee, Shoulder)

•   The side that will be operated on (Left, Right, Both)

•   Patient contact details such as phone number and email address

We believe this request satisfies the criteria as detailed in the National Statement on Ethical Conduct in Human Research (2007 (updated 2018), chapter 2.3) for providing a waiver of consent. This waiver of consent is only for collecting information through the registration process and not to the completion of the PROMs instruments.

As explained in the protocol, if registered patients do not consent, then all their identifying information will be deleted from the PROMs database.

   a) involvement in the research carries no more than low risk

   • This is a low risk project particularly as the waiver is specifically required to defer involvement in the project after the registration as a mechanism to ensure that patients that take this option can complete their involvement in the project at a time that is most suitable to them.

   b) the benefits from the research justify any risks of harm associated with not seeking consent

   • There is no risk of harm associated with storing the patient's details prior to collecting consent. The Registry will receive almost all of this data at the time of the procedure. It is being requested to enhance participant convenience. The AOANJRR is a declared Federal

Quality Assurance Activity and all data is managed in accordance with that declaration which includes the use of high-level security systems.

c) it is impracticable to obtain consent (for example, due to the quantity, age or accessibility of records)

- It is not feasible to collect patient consent prior to the registration as it is necessary to link the electronic consent to the individual patient identified by the registration process. If the consent is completed prior to registration, then the consent will be unidentified.

d) there is no known or likely reason for thinking that participants would not have consented if they had been asked

- Patients will verbally consent to have their details recorded at registration and this will be subsequently confirmed prior to completion of the PROMs instruments. It is the AOANJRR experience that very few patients are reluctant to have their data included in the Registry.

e) there is sufficient protection of their privacy

- The AOANJRR is a declared Federal Quality Assurance Activity

- Systems are in place to ensure individual patient data remains confidential

- A third-party security review and penetration testing has been undertaken on the AOANJRR clinical trials electronic system

f) there is an adequate plan to protect the confidentiality of data

- The South Australian Health and Medical Research Institute (SAHMRI) is the organisation responsible for managing AOANJRR data and has existing security systems, policies and procedures in place as well as software barriers to protect personal information and ensure confidentiality. These systems are already in place for data contained within the AOANJRR and the data collected for the registry-nested study will be treated identically.

g) in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (for example, via a disease-specific website or regional news media)

- Results from the study will be published publicly in peer-reviewed journals.

h) the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled

- The AOANJRR is a not for profit organisation which does not use the data it collects for commercial gain.

i) the waiver is not prohibited by State, federal, or international law

- There are no applicable laws prohibiting this waiver.

16.2 Withdrawal

Participation is voluntary and participants are free to withdraw from the study at any time. They will be reassured that their medical care will not be affected by their decision to withdraw. Upon withdrawal, subjects will not be contacted for follow-up. If they have not requested removal from Registry data, revision data will still be included as part of the outcome assessment. If the patient elects to withdraw at the time of their postoperative assessment, then no further follow-up will be undertaken.

17 Data Confidentiality, Privacy and Security

Data will be collected and stored in the AOANJRR database within South Australian Health and Medical Research Institute (SAHMRI) [63] which is protected by the Quality Assurance Activity (QAA) legislation of the Health Insurance Act of 1973. The protection ensured by the QAA declaration assures patients, surgeons, hospitals and government that information supplied to the AOANJRR remains confidential and secure (www.aoanjrr.sahmri.com/governance). SAHMRI will provide information technology (IT), data management and statistical analysis services for this registry-nested study. SAHMRI is contracted by the AOA to provide similar services for the AOANJRR. This collaboration has been very successful at maintaining a high level of data security and data quality for the AOANJRR.

17.1 South Australian Health and Medical Research Institute

SAHMRI is South Australia's first independent flagship health and medical research institute. The SAHMRI team working on the AOANJRR consists of a project manager, data managers, statisticians, IT resources and data entry staff. The SAHMRI team contribute crucial data management and analysis expertise to the AOANJRR which will be transferred to the RASKAL study. This collaboration has been very successful at maintaining a high level of data security and data quality for the AOANJRR. See SAHMRI ICT Security Summary (Appendix 6).

17.2 Protection and confidentiality

The AOANJRR is required to have highly secure data protection systems to secure the identified information which it currently holds as this is an absolute requirement under its Federal Quality Assurance Activity. SAHMRI has existing security systems, policies and procedures in place as well as software barriers to protect personal information and ensure confidentiality.

The RAPID platform used to collect PROMs had a third-party security review of the infrastructure and application design undertaken prior to development, as well as a penetration test of the application prior to commencement of data collection. As further enhancements to the RAPID platform take place, external penetration tests are planned to be regularly undertaken as recommended by SAHMRI ICT.

17.3 Restrictions to use of data

The data collected as part of standard Registry data collection will continue to be used for Registry activities, any additional data collected specifically for this study will only be used by the AOANJRR for the purposes of this study. Any data published in reports, papers and publications will be de-identified. Access to identifiable information is limited to authorised AOANJRR and SAHMRI staff.

17.4 Patient confidentiality

All patient data will be managed in accordance with the Guidelines for the Protection of Privacy in the Conduct of Medical Research. Patient contact details will only be used for the purpose for which they were collected and will be stored securely and confidentially. Only patients and their operating surgeon (when consent is provided) will have access to their own results via the online application. Patients will not be identified in any reports, manuscripts or presentations derived from the RASKAL project. https://www.oaic.gov.au/privacy/the-privacy-act/rules-and-guidelines/medical-research/

17.5 Surgeon confidentiality

Surgeons will only be able to review the PROMs data of patients where they undertook the surgery. No individual surgeons will be identified in any reports produced or any online dashboard except their own.

18 Data Storage and Record Retention

The SAHMRI Data Management Staff have established security systems which limit access to SAHMRI Data Management and Registry staff only. There are policies and procedures in place as well as software barriers to protect personal information. These include the use of codes, passwords and encryption. Proformas used for data collection will be stored in a secure locked room at SAHMRI. After a period of two years the forms stored will be optically scanned and electronically stored in the secure SAHMRI database. All data will be retained in accordance with good scientific practice. All electronic data collected will be held for a minimum of 15 years after publication of any final reports and manuscripts.

19 Reporting and Dissemination

The results of this research will be presented at national and international orthopaedic surgical meetings such as the Australian Orthopaedic Association Annual Scientific Meeting, the Arthroplasty Society of Australian Annual Meeting, the Australian Knee Society Annual Meeting, and the American Academy of Orthopaedic Surgeons. We aim to have this research submitted to a high impact journal for publication. It is anticipated that the results of this trial will inform future clinical practice and surgical guidelines.

20 Governance

All surgical and research contributors will be part of the RASKAL Study Group. A Writing Group and a Working Group will be established to manage manuscript preparation and the day-to- day management of the trial, respectively. Authorship will be by the Writing Group on behalf of the RASKAL Study Group.

21 Funding

Application for research grants will be submitted to the Ramsay Hospital Research Fund (RHRF) and the Australian Orthopaedic Association Research Fund (AOARF). Funding is intentionally not being sought from implant manufacturers to maintain independence over study design, analysis and interpretation of results. Research funds will be managed by the AOA. Research physiotherapists will be employed to undertake functional assessments. A local research coordinator will be recruited at each site to provide patient education, assist in obtaining consent, support hospital staff and collect perioperative data. Research officers will complete online Good Clinical Practice (GCP) training. A compliance officer will be recruited to randomly review sites and surgical procedures in order to ensure the study protocol is being adhered to.

Appendix 1. Detailed Surgical Protocol for RASKAL Study

General Surgical Principles

1. <u>Anaesthesia</u> – Spinal anaesthesia, epidural anaesthesia, GA, or combined permissible.

2. <u>Tourniquet Use</u> – Surgeon preference (not used / partial use / full use).

3. <u>Surgical approach</u>
   - Medial parapatellar arthrotomy
   - Minimal medial elevation of capsule to mid sagittal plane
   - Resection of ACL prior to pre-resection knee gap balancing

4. <u>Prosthesis</u>
   - Implant system
     - Stryker Triathlon cruciate-retaining (CR) system
   - Implant fixation
     - Fully cemented femoral and tibial components in all cases
   - Patella
     - Routine resurfacing with oval onlay cemented implant in all cases unless maximal pre-resection bone thickness ≤ 15mm
   - Stability
     - CR articular insert in all cases
     - Conversion to cruciate-substituting (CS) or posterior-stabilised (PS) permitted only if PCL found to be incompetent

5. <u>Alignment Systems</u>
   - Computer-Assisted Surgery (CAS) system – Precision-3 full optical
   - Robotic-Arm Assisted Surgery (RAS) system - MAKO

6. <u>Alignment Definitions and Landmarks</u>
   - *Mechanical Alignment (MA)*: standardised positioning of implants relative to fixed non-articular anatomic landmarks to recreate a neutral hip-knee-ankle (HKA) angle, neutral joint line obliquity (JLO) with compensatory femoral component external rotation.
   - *Kinematic Alignment (KA)*: individualised positioning of implants based off articular landmarks within a restricted boundary alignment protocol. As the RAS-KA group also includes pre-resection gap balancing, and both CAS-KA and RAS-KA have alignment boundaries, final implant positioning may more closely approximate a *"functional position" (Oussedik et al BJJ March, 2020)* in some study participants. The term KA however will be used for these two study groups, however it is recognised adjustments towards a non-anatomically resurfaced, functional position from gap balancing and restricted alignment boundaries may result.
   - *Femoral mechanical axis:* The line connecting the hip centre to the femur knee centre.

- *Surgical Transepicondylar Axis (TEA):* line connecting lateral epicondylar eminence and the medial epicondylar sulcus.
- *Tibia Mechanical Axis:* line connecting the 'tibia knee centre' to the 'ankle centre'. 'Ankle Centre' is computed from the collection of the medial and lateral malleoli landmarks. The malleoli landmarks are located on the outermost bony protuberances.
- *Tibia Anteroposterior (AP) Axis*: a line connecting the PCL centre to the medial border of the patellar tendon.
- *Tibia Mediolateral (ML) Axis*: The 'Tibia ML Axis' is perpendicular to the 'Tibia AP Axis'.
- *Arithmetic hip-knee-ankle angle (aHKA)*: an estimation of constitutional (pre-arthritic) knee alignment derived from subtracting the lateral distal femoral angle (LDFA) from the medial proximal tibial angle (MPTA) *(Bone Joint Open July, 2020.)*

7. <u>Sizing of implants</u>
   - The femoral implant is to be within 1 size of the tibial implant.
   - Sizing of the femur is determined by:
     - restoring AP dimensions with anterior cut run out to exit at tip of implant
     - maximising ML coverage without overhang
     - matching constitutional medial femoral condylar radius of curvature to implant femoral component (RAS arms)
     - restoring trochlear depth (RAS arms)
   - The tibial implant, once aligned to the tibial AP axis, is to be sized for maximal ML coverage without overhang in any region. Downsizing may be required, whilst ensuring femoral-tibial implant matching.
   - The patellar implant size is to be determined with the largest implant that reaches either the proximal-distal or ML cortical rim without overhang.

8. <u>Computed Tomographic (CT) Imaging and Intraoperative CAS Resection Landmarks</u>
   - Distal femoral resection landmarks:
     - The distal resection landmarks are located on the most distal point of the medial and lateral distal condyles, avoiding osteophytes.
   - Posterior resection landmarks:
     - The posterior resection landmarks are located on the most posterior aspect of the medial and lateral distal condyles, avoiding osteophytes.
   - Tibia resection landmarks:
     - Location approximately 2/3 posterior AP distance of the medial and lateral plateau, such that the landmarks are near the insert low point.
     - Points to lie in the same approximate sagittal plane and are centered in the medial and lateral compartments in the coronal plane.

9. Initial resection angles
   - CAS-MA and RAS-MA groups
     - All resection angles to be based off fixed angular resections as per group Summary Tables.
     - Femoral sagittal resection angle is variable (0-6°) with start point of 5° for females and 3° for males.
   - CAS-KA and RAS-KA groups
     - Initial resection angles determined by:
       - **CAS-KA:** *Preoperative* bilateral long-leg weight bearing radiographs used for planning
       - **RAS-KA:** *Intraoperative* CT-based planning using matched resections in MAKO planning screen.
     - CAS-KA measurements determined by blinded study radiographer and validated by orthopaedic surgeon investigator who is not part of the RASKAL surgeon group.
     - Operative plan provided will include:
       - Lateral distal femoral angle (LDFA)
       - Medial proximal tibial angle (MPTA)
       - mechanical HKA (angle subtended by mechanical axes of femur and tibia on long-leg radiographs)
       - aHKA
       - Femoral Coronal Resection Angle (FCRA)
       - Tibial Coronal Resection Angle (TCRA)
       - Tibial Sagittal Resection Angle (TSRA)
       - Femoral Rotation Resection Angle (FRRA)
     - Femoral Sagittal Resection Angle (FSRA) is variable (0-6°) with start point of 5° for females and 3° for males.
     - Tibial Rotation Angle (TRA) is centred on AP axis from centre of PCL footprint to medial border patellar tendon.

10. Final alignment targets
    - Validated implant position: aim to be within +/- 1 degree of alignment targets for MA groups and adjusted (pre-resection) targets for KA groups.
    - Final HKA: aim to be within +/- 1-degree boundary, then:
      - accept and record if within +/- 2 degrees for target HKA.
      - if outside this then aim to correct to bring within +/- 2 degrees.
    - Final knee flexion angle: To be within +/- 3 degrees of full extension.

11. Initial and definitive alignment measurements
    - In all four groups, the following alignments will be recorded:
      - adjusted (pre-resection) resection angles if different from initial plan (FCRA, TCRA, FSRA, TSRA, FRRA)
      - validated resection angles (FCRA, TCRA, FSRA, TSRA, FRRA)
      - final HKA and final knee flexion angle with definitive polyethylene insert in situ

12. <u>Sensor compartmental load measurements</u>
- After cementation of definitive femoral and tibial prostheses, and prior to insertion of definitive articular insert, the Verasense pressure sensor instrument (Orthosensor, FL, USA) of the same final size and articular thickness will be inserted.
- Two towel clips will approximate the extensor mechanism.
- Surgeon is to be blinded to measurements with screened turned away from surgical field.
- Measurements will be recorded at 10°, 45° and 90°.
- The insert will be removed after the first measurements, the insert recalibrated, and measurements will be repeated.
- The mean of the 2 measures will be used.
- If the research officer believes that the sensor has an "overload" error, the surgeon will be asked to recalibrate the sensor.

1. Computer-Assisted Surgery and Mechanical Alignment (CAS-MA) Group

Rationale: CAS-MA serves as the control for both factorial groups. Coronal bone resections are performed perpendicularly to the MA of the femur and tibia. Rotation of the femoral component parallel to the surgical TEA and perpendicular to the femoral AP axis.

Balancing Methodology:
- Soft tissue releases only. No bone alignment adjustments are allowed.
- Use of gap balance data provided by CAS is allowed to undertake knee balancing.

CAS-MA Summary Table:

Parameter	Alignment Targets
HKA Angle	0°
Femoral Coronal Resection Angle	0°
Femoral Sagittal Resection Angle	0°-6°
Femoral Rotational Resection Angle	Primary - Parallel to surgical TEA and perpendicular to femoral AP axis (mean value of these 2 variables as per Precision software) Secondary- 3° ER to posterior condylar axis (PCA)
Tibial Coronal Resection Angle	0°
Tibial Sagittal Resection Angle	3° posterior slope
Tibial Rotational Angle	Tibial AP Axis - Centre of PCL footprint to medial border patellar tendon
Combined Sagittal Resection Angle (FSRA + TSRA)	If tibial size < femoral size, 8°combined flexion If tibial size ≥ femoral size, 10° combined flexion
Resection Depths (In CAS arms, resections depths based off cartilage)	Medial distal femoral resection – 8mm if no significant chondral wear, 6mm if worn to subchondral bone. (Note 6mm for RAS-MA group). The lateral distal femoral resection is resultant. This is based on the assumption that the medial side, which is also the worn side in varus knees is the high side. Posterior medial femoral resection – 8mm if no significant chondral wear, 6mm if worn to subchondral bone. (Note 6mm for RAS-MA). The lateral posterior femoral resection is resultant. This is based on the assumption

	that the posteromedial condyle has minimal cartilage wear in the varus knee. <u>Proximal lateral tibial resection</u>– 9mm thickness for varus knee (note 7mm for RAS-MA). For valgus knees, 7mm thickness off medial plateau (note 5mm for RAS-MA)
Knee Balancing at 10° and 90°	Soft tissue releases only Aim to achieve gap asymmetry ≤ 2mm
Balancing Method	Soft tissue release algorithm - Medial tightness in extension → pie-crust posterior fibres MCL at 10° then semimembranosus and posteromedial capsule release - Medial tightness in flexion → pie-crust anterior fibres MCL at 90° - Lateral tightness in extension → release arcuate ligament followed by ITB - Lateral tightness in flexion → release popliteus off femur followed by LCL
Final Extension Range of Motion	+/- 3 degrees of full extension

<u>Operative Technique:</u>

1. Remove osteophytes, resect ACL

2. Perform CAS Registration of bony landmarks
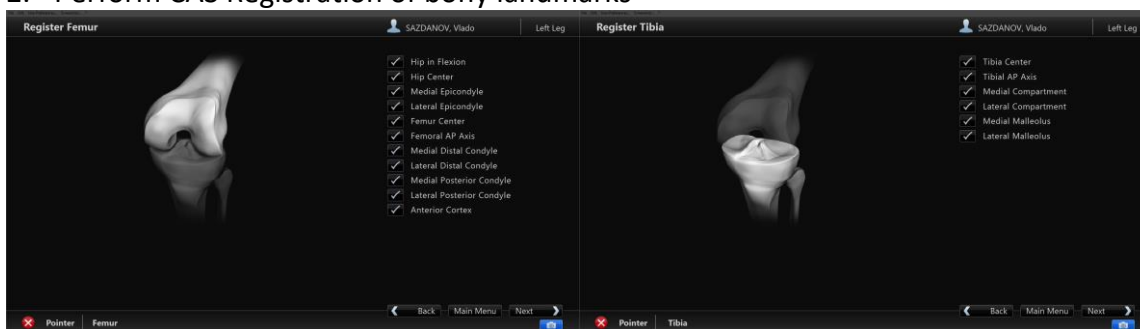
3. Record the following alignments with extensor mechanism clipped
    - Resting HKA
    - Knee flexion angle
    - Corrected (stressed) alignment with knee 10° (+/- 5°)
    - Record flexion stress curve

4. Set Femoral Positions at "Modify Implant Position Screen"
    - Input 0° femoral coronal angle (Var./Val.)
    - Input 0° femoral rotational angle (Flex. Var./Val)
    - Adjust implant size
    - Adjust femoral flexion angle for best implant fit
    - Adjust femoral AP and PD shift to achieve resection depth targets

5. Perform and validate distal femoral resection

6. Perform and validate tibial resection

7. Insert 17mm spacer block into extension space and check
- HKA target of 0° achieved
- Knee extension adequate
  - Aim ≤5° flexion at this stage
  - *Only consider* 2mm distal femoral resection if navigated FFD> 10°
  - *Only consider* 2mm proximal tibial resection if all of the following present:
    i. navigated FFD 6-10°
    ii. femoral resection thicknesses at least 8mm on high side
    iii. flexion space also tight with use of 9mm space block
    iv. volume of posterior osteophytes not significant (ie FFD would likely improve with removal of large osteophytes)

8. Complete and validate 4-in-1 femoral resections

9. Trial implants
- Maximum size articular insert to achieve extension (0°+/- 3°)
- Perform gap balance assessment in extension
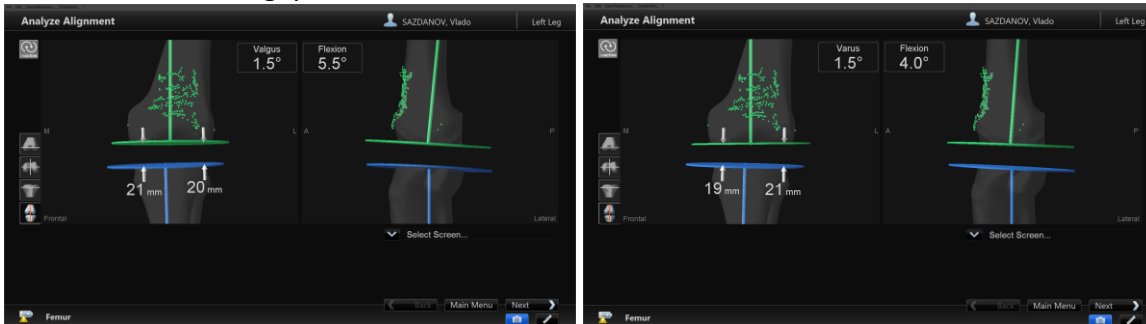
- Perform gap balance in flexion
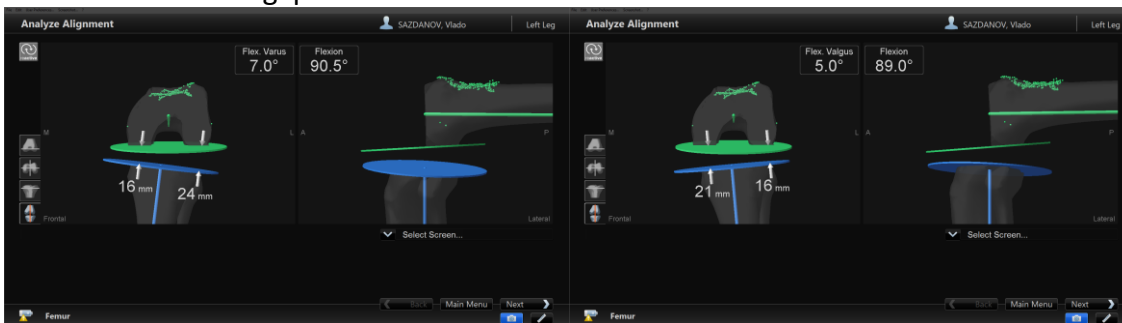
9. Soft tissue balancing as per CAS-MA Summary Table if required

10. Insert definitive femoral, tibial and patellar implants
- Measure sensor pressures twice with screen turned away from surgeon to maintain blinding
- Insert definitive articular insert and record final HKA and knee extension angle

2. Computer-Assisted Surgery and Kinematic Alignment (CAS-KA) Group

Rationale: The CAS-KA cohort represents a restricted boundary KA technique. The surgeon will be provided with a plain-radiographic preoperative KA plan, as CAS is considered an imageless (non-CT derived) technique.

Balancing Methodology:
- Initial balance assessment once osteophytes removed and navigation planning undertaken.
- Adjustments permitted to initial KA start plan and will be recorded.

CAS-KA Summary Table:

Parameter	Alignment Targets
HKA Angle	6° varus to 3° valgus
Femoral Coronal Resection Angle	6° valgus to 3° varus
Femoral Sagittal Resection Angle	0° to 6° flexion
Femoral Rotational Resection Angle	Boundaries: -6° IR to + 6° ER to surgical TEA Set parallel to posterior condylar axis (0° to PCA assuming cartilage intact). Adjusted if needed according to balancing protocol
Tibial Coronal Resection Angle	6° varus to 3° valgus
Tibial Sagittal Resection Angle	0° to 6° flexion
Tibial Rotational Angle	Tibial AP Axis - Centre of PCL footprint to medial border patellar tendon
Combined Sagittal Resection Angle (FSRA + TSRA)	If tibial size < femoral size, 8° combined flexion If tibial size ≥ femoral size, 10° combined flexion
Resection Depths	Maximal distal femoral resection – 8mm (note 6.5mm for RAS-KA) off highest side depending on osteochondral wear pattern. Resections will be equal if similar depth of cartilage loss on both condyles. Maximal posterior femoral resection – 8mm (note 6.5mm for RAS-KA). Resections will be equal if similar depth of cartilage loss on both condyles. Proximal lateral tibial resection - 9mm resection set off chondral surface of highest plateau (usually lateral) in varus knee to create a resection plane parallel to the patient's tibial joint line (7mm for RAS-KA due to bone surface reference). For valgus knees, 7mm thickness off medial plateau (note 5mm for RAS-KA).

Acceptable stressed gap differences (minimum non-stressed 20mm gaps)	10°: Lateral gap 0-2mm ≥ medial gap 90°: Lateral gap 0-6mm ≥ medial gap
Knee Balancing	1. bony recut for >2mm gap asymmetry in extension • Consider 1-2° tibial angular correction for unicompartmental tightness if gap asymmetry > 2mm at 10°, and >6mm at 90° • Consider 1-2° femoral angular correction if not balanced at 10° only 2. Consider soft tissue release • if reached restricted alignment boundaries reached for HKA, implant or both • unicompartmental tightness in flexion only (to avoid change in 4-1 cuts) 3. Soft tissue release algorithm • Medial tightness in extension → pie-crust posterior fibres MCL at 10° then semimembranosus and posteromedial capsule release • Medial tightness in flexion → pie-crust anterior fibres MCL at 90° • Lateral tightness in extension → release arcuate ligament followed by ITB • Lateral tightness in flexion → release popliteus off femur followed by LCL
Final Extension Range of Motion	+/- 3 degrees of full extension

Operative Technique:

1. Remove osteophytes, resect ACL

2. Perform CAS Registration of all bony landmarks
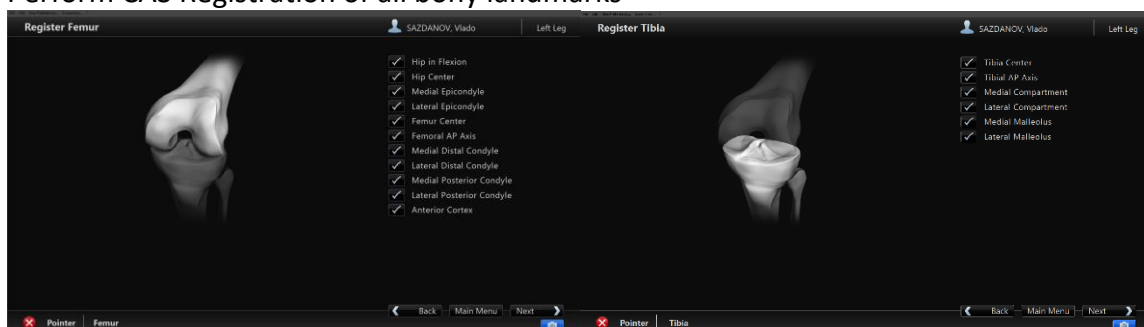
3. Record the following alignments with extensor mechanism clipped
   - Knee flexion angle
   - Resting HKA
   - Corrected (stressed) alignment with knee 10° (+/- 5°)
     - Check if corrected (stressed gap) in extension approximates aHKA and final target HKA. Usually corrected alignment is 1-2 degrees greater than aHKA.
     - This indicates that combined distal femoral and proximal tibial resections should restore extension gap balance (MPTA minus LDFA).
   - Record flexion stress curve

4. Adjust femoral and tibial coronal resection angles based on stressed HKA:
   - Stressed HKA (over aHKA) is the final determinant of target alignment
   - If stressed HKA = aHKA within +/- 2 degrees, then use FCRA and TCRA as per preop plan.
   - If stressed HKA < aHKA (more varus), then increase TCRA into varus.
     - Eg if stressed HKA = -5 degrees varus, aHKA = -2 degrees varus, then increase planned tibial resection by a further 3 degrees of varus without exceeding TCRA boundaries.
   - If stressed HKA > aHKA (more valgus), then increase FCRA into valgus.
     - Eg if Stressed HKA = 2 degrees valgus, aHKA = -1 degrees varus, then increase planned femoral resection by a further 3 degrees of valgus without exceeding FCRA boundaries.

5. Set Femoral Positions at "Modify Implant Position Screen"
   - Input femoral coronal angle (Var./Val.) as per adjusted CAS-KA plan.
   - Alter femoral rotational angle (Flex. Var./Val) to obtain symmetrical 8mm posterior resections. This aligns the implant to PCA (as PCA not provided). Record subsequent angle relative to surgical TEA.
   - Adjust implant size.
   - Adjust femoral flexion angle for sizing (0-6°) and fit.
   - Adjust femoral AP and PD shift to achieve resection depth targets.
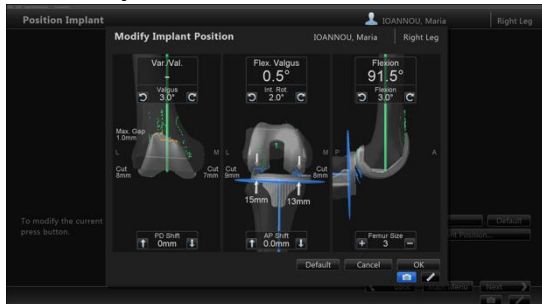
6. *Check corrected extension gap* to confirm resection angle. Gap differential should act as a measure for tibial resection angle.
   - Eg, if in extension, medial gap 19mm, lateral gap 19mm, then planned tibial coronal resection angle should be 0°.
   - Eg, if medial gap 16mm, lateral gap 19mm, then planned TCRA estimation likely 3° varus.

7. Perform and validate distal femoral resection

8. Complete and validate proximal tibial resection

9. Insert 17mm spacer block into extension space and check:
   - HKA target achieved
   - Knee extension adequate
     - Aim minimum 5° flexion at this stage, depending on volume of posterior osteophytes
     - *Only consider* symmetric 2mm distal femoral resection if navigated FFD> 10°
     - *Only consider* symmetric 2mm proximal tibial resection if all of the following are present: 1. navigated FFD 6-10°, 2. femoral resection thicknesses at least 8mm, and 3. volume of posterior osteophytes not significant.
   - Varus-valgus stressed gaps relative to ideal gaps

10. Insert 9mm spacer block into flexion space and assess flexion stressed gaps relative to ideal gap values.

11. Complete 4-in-1 femoral resections
    - Check flexion knee balance with 9mm spacer
      - no adjustment needed if gaps 19-25mm lateral; 19mm medial
    - Use of femoral sizing guide set to 0° to PCA (can also navigate position aiming for 8mm matched posterior resections) if cartilage intact on both posterior condyles. Adjust rotation to match discrepancies in asymmetric cartilage loss.
    - Pin cutting block
    - Check 4-in-1 cutting guide alignment prior to resections being performed
    - Validate resection angles (FSRA, FRRA)
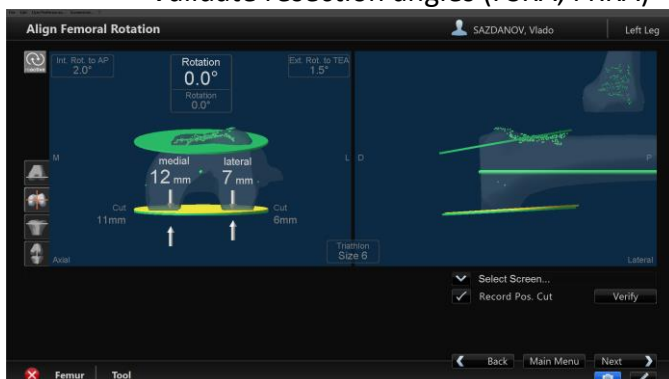
12. Trial implants
   - Maximum size insert to achieve extension (0°+/- 3°)
   - Perform gap balance assessment in extension
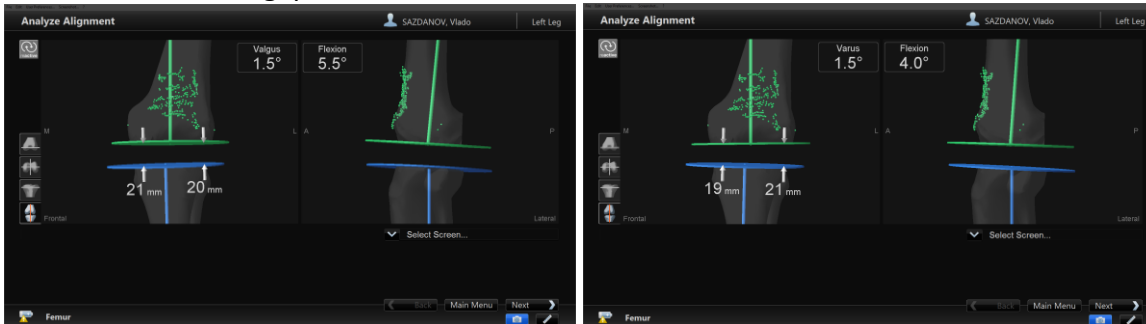
   - Perform gap balance in flexion
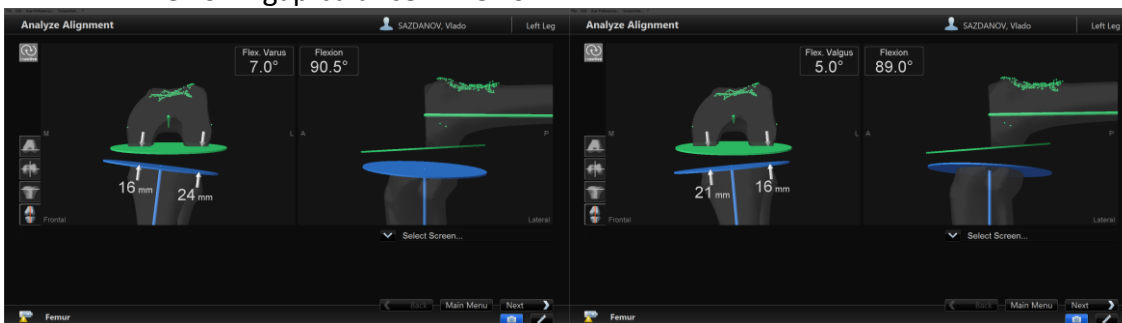
13. Balance knee as per CAS-KA Summary Table if required.

14. Insert definitive femoral, tibial and patellar implants
   - Measure sensor pressures twice with screen turned away from surgeon to maintain blinding
   - Insert definitive articular insert and record final HKA and knee flexion angle

3. Robotic-Assisted Surgery and Mechanical Alignment (RAS-MA) Group

Rationale: RAS-MA is the second control group for comparison against KA. In addition, this factorial group will test whether RAS haptic boundaries reduce postoperative analgesia consumption and improves early patient outcomes due to a reduction in soft tissue trauma compared to CAS-MA. Preoperative planning software will be set to the MA alignment targets below. Only adjustment of femoral sagittal position is allowed to optimise femoral component ML bone coverage, AP position and size.

Knee Balancing:
- Manual balancing will be performed with soft tissue releases only. Not bone alignment readjustments allowed.
- Use of gap balance data provided by RAS is allowed to achieve knee balance.

RAS-MA Summary Table:

Parameter	Alignment Targets
HKA Angle	0°
Femoral Coronal Resection Angle	0°
Femoral Sagittal Resection Angle	0°-6°
Femoral Rotational Resection Angle	Primary - Parallel to surgical TEA
Tibial Coronal Resection Angle	0°
Tibial Sagittal Resection Angle	3°
Tibial Rotational Angle	Tibial AP Axis - Centre of PCL footprint to medial border patellar tendon
Combined Sagittal Resection Angle (FSRA + TSRA)	If tibial size < femoral size, 8° combined flexion If tibial size ≥ femoral size, 10° combined flexion
Resection Depths	Medial distal femoral resection – 6mm off subchondral bone (note 8mm for CAS-MA assuming cartilage intact). The lateral distal femoral resection is resultant. Posterior medial femoral resection – 6mm off subchondral bone (note 8mm for CAS-MA assuming cartilage intact). The lateral posterior femoral resection is resultant. Proximal lateral tibial resection– 7mm thickness for varus knee (note 9mm for CAS-MA). For valgus knees, 5mm thickness off medial plateau (note 7mm for CAS-MA)
Knee Balancing at 10° and 90°	Soft tissue releases only Aim to achieve gap asymmetry ≤ 2mm
Balancing Method	Soft tissue release algorithm

	• Medial tightness in extension → pie-crust posterior fibres MCL at 10° then semimembranosus and posteromedial capsule release • Medial tightness in flexion → pie-crust anterior fibres MCL at 90° • Lateral tightness in extension → release arcuate ligament followed by ITB • Lateral tightness in flexion → release popliteus off femur followed by LCL
Final Extension Range of Motion	+/- 3 degrees of full extension

Operative Technique:

1. Preoperative input of MA start plan

2. Resect ACL, menisci

3. Perform RAS Bone Registration

4. Remove osteophytes

5. Record the following alignments with extensor mechanism clipped
   - Resting HKA
   - Knee flexion angle
   - Corrected (stressed) alignment with knee at 10° (+/- 5°)

6. Perform and record virtual gap balancing at 10° and 90°

7. Perform robotic-arm assisted MA femoral and tibial resections and validate cuts

8. Trial implants
   - Maximum size insert to achieve extension (0°+/- 3°)
   - Perform gap balance assessment in extension
   - Perform gap balance assessment in flexion

9. Soft tissue balancing as per RAS-MA Summary Table if required

10. Insert definitive femoral, tibial and patellar implants
    - Measure sensor pressures twice with screen turned away from surgeon to maintain blinding
    - Insert definitive articular insert and record final HKA and knee flexion angle

4. Robotic-Assisted Surgery and Kinematic Alignment (RAS-KA) Group

Rationale: RAS-KA is the intervention arm for both surgical assistance and alignment groups. Alignment in this group is set intraoperatively by MPS and surgeon using matched resections. The only adjustments to the matched resections start plan is if restricted KA boundaries are exceeded. Secondary functional implant positioning is achieved by virtually gap balancing of the knee prior to bone resections.

RAS-KA Summary Table:

Parameter	Alignment Targets
HKA Angle	6° varus to 3° valgus
Femoral Coronal Resection Angle	6° valgus to 3° varus
Femoral Sagittal Resection Angle	0°-6° flexion
Femoral Rotational Resection Angle	Boundaries -6° IR to + 6° ER to surgical TEA Primary -set parallel to PCA (using 6.5mm matched resections) then adjusted according to intraoperative gap balancing targets
Tibial Coronal Resection Angle	6° varus to 3° valgus
Tibial Sagittal Resection Angle	0-6 flexion° matched to lateral tibial plateau
Tibial Rotational Angle	Tibial AP Axis - Centre of PCL footprint to medial border patellar tendon
Combined Sagittal Resection Angle (FSRA + TSRA)	If tibial size < femoral size 8° combined flexion If tibial size ≥ femoral size, 10° combined flexion
Initial Resection Depths and Preoperative Plan	Distal femur – Matched 6.5mm resections set off the medial and lateral distal condyles to create a resection plane parallel to the patient's femoral joint line. The resulting femoral component coronal angulation is patient specific. Posterior femur – Matched 6.5mm resections set off the medial and lateral posterior condyles to create a resection plane parallel to the patient's posterior condylar axis. The resulting femoral component coronal angulation is patient specific. Proximal tibia – Matched 7mm resections will be set off the medial and lateral proximal tibial plateau to create a resection plane parallel to the patient's tibial joint line. The resulting tibial component coronal angulation is patient specific.

Virtual Gap Balancing Targets	Ideal Gaps		
		Medial	Lateral
	Extension	20	20
	Flexion	20	20-26 (patient specific)
	Minimum Acceptable Gaps		
		Medial	Lateral
	Extension	20	20
	Flexion	20	20
	Maximum Acceptable Gaps		
		Medial	Lateral
	Extension	20	21
	Flexion	20	26

Final Virtual Gap Balancing	1. bony recut for >2mm gap asymmetry in extension
	• Consider 1-2° femoral angular correction if not balanced at 10° only
	• Consider 1-2° tibial angular correction for unicompartmental tightness if gap asymmetry > 2mm at 10°, and >6mm at 90°
	2. Consider soft tissue release
	  a. if reached restricted alignment boundaries for HKA, implant or both
	  b. unicompartmental tightness in flexion only
	3. Soft tissue releases
	• Medial tightness in extension → pie-crust posterior fibres MCL at 10° then semimembranosus and posteromedial capsule release
	• Medial tightness in flexion → pie-crust anterior fibres MCL at 90°
	• Lateral tightness in extension → release arcuate ligament followed by ITB
	• Lateral tightness in flexion → release popliteus off femur followed by LCL

Final Extension Range of Motion	+/- 3° of full extension

Operative Technique:

1. Intraoperative input of KA matched resections and record FCRA, TCRA, and FRRA (relative to sTEA)

2. Resect ACL, menisci

3. Perform RAS Bone Registration

4. Remove osteophytes

5. Record the following alignments with extensor mechanism clipped
   - Resting HKA
   - Knee flexion angle
   - Corrected (stressed) alignment with knee 10° (+/- 5°)

6. Perform virtual gap balancing by adjusting resection angles and depths as per Surgical Summary Table
   - Gap balancing will occur to, but not exceed, alignment boundaries
   - *Achieve extension gap balance first*
     - Ideal extension target gaps 20mm lateral; 20mm medial
     - Most common scenario to balance extension gap is to alter TCRA (usually increasing varus) by locking centre of rotation laterally. This will also assist in balancing flexion gap as this most commonly tighter medially
     - Adjust FCRA if extension gap imbalance only
     - Avoid reducing femoral valgus (increasing LDFA) by more than 2° to minimise lateral column lengthening
   - *Flexion gap balance*
     - Aim for matched medial gaps of 20mm in extension and flexion
     - Most common scenario is medial gap tightness. Lock centre of rotation laterally and externally rotate.
     - Flexion target gaps 20-26mm lateral; 20mm medial
   - Due to vast combinations of alignment adjustments that can lead to a functionally balanced knee, no prescribed algorithm will be enforced; rather there will be a reliance on surgeon expertise, aiming to preserve coronal joint line obliquity in extension in the balancing process as well as following above principles.

7. Perform robotic-arm assisted femoral and tibial resections and validate cuts.

8. Trial implants
   Maximum size insert to achieve extension (0°+/- 3°)
   Perform gap balance assessment in extension
   Perform gap balance assessment in flexion

9. Balance knee as per RAS-KA Summary Table if required.

10. Insert definitive femoral, tibial and patellar implants
    - Measure sensor pressures twice with screen turned away from surgeon to maintain blinding
    - Insert definitive articular insert and record final HKA and knee flexion angle

Appendix 2. In-Hospital Monitored Complications.

Adverse Event (AE)	AE Description	Event Occurred (tick only if yes)	Additional Notes
SSI requiring antibiotics only	Any antibiotic taken for surgical site beyond standard post-op IV dosing regime		
SSI requiring surgery superficial to joint (e.g. wound dehiscence)	Any surgery for a wound complication that does not require entering the joint and associated liner exchange		
Deep vein thrombosis	Must be symptomatic + Doppler U/S proven DVT		
Pulmonary Embolus	Must be proven PE on CTPA or V/Q scan		
Drug Reaction - Anaphylaxis	Medication induced anaphylaxis (meds related to TKA)		
- Delirium/Confusion	Acute confusion or delirium during the in-hospital stay		
Cardiovascular Events	Changes in ECG, troponin or advanced scans		
Respiratory Infection	Changes on chest x-ray in conjunction with clinical findings		
Urinary tract Infection	Positive urine culture with symptoms		
Urinary Retention	> 500mls on bladder scan		
In Hospital Fall	Documented fall in patients notes		
Nerve Injury	Clinical disruption of nerve function		
Return to Theatre (all causes)	Any documented return to theatre for miscellaneous causes (e.g. retained foreign body, patella facetectomy, extensor mechanism disruption)		
Death (all causes)	Any death related or unrelated to the TKA		

Appendix 3. Schedule of Collected Study Items and Assessments

Collected Item	Preoperative	Inpatient	3 & 6 weeks	3 months	6 months	1 year	2 years
Visit window				+3 weeks/	+2 months/	±2 months	±3 months
Recruitment and consent	X						
Demographics	X						
Intra and postoperative data		X					
KOOS-12	X			X	X	X	X
Visual Analogue Scale (VAS) Pain	X		X	X	X	X	X
Oxford Knee Score (OKS)	X		X	X	X	X	X
Forgotten Joint Score 12 (FJS-12)	X			X	X	X	X
EQ-5D-5L (EuroQoL)	X			X	X	X	X
Analgesia	X		X	X			
Patient Satisfaction				X	X	X	X
Patient Rated Joint Change				X	X	X	X
Patient Reported Complications		X	X	X			
Functional Assessments					X		
Knee Range of Motion	X				X		
Plain Radiographs	X	X				X	X
MAKO CT Protocol	X						
Postoperative CT Perth Protocol		X					
Adverse Event Reporting		X	X	X	X	X	X

PROMs = patient-reported outcome measures of KOOS, VAS, Oxford, FJS, EQ5D-5L Satisfaction; CT = computed tomographic scan

Appendix 4. Complete Study Complication List and Reporting Identification Process

Complication Monitoring Period	Adverse Event	SAE Reportable Event (Y/N)	Identification Process	Description
0-3 Months	SSI requiring antibiotics only	N	1° Project Officer 2° Surgeon	Any antibiotic taken for surgical site beyond standard postop IV dosing regime
	SSI requiring surgery superficial to joint (e.g. wound dehiscence)	Y	1° Surgeon 2° Project Officer	Any surgery for a wound complication that does not require entering the joint and associated liner exchange
	Deep vein thrombosis	N	1° Project Officer 2° Surgeon	Must be symptomatic + Doppler U/S proven DVT
	Pulmonary Embolus	Y	1° Project Officer 2° Surgeon	Must be proven PE on CTPA or V/Q scan
	Drug Reaction			
	• Anaphylaxis	Y	1° Surgeon 2° Project Officer	Medication induced anaphylaxis (meds related to TKA)
	• Delirium/Confusion	N	1° Project Officer 2° Surgeon	Acute confusion or delirium during the in-hospital stay
	Cardiovascular Event	Y	1° Project Officer 2° Surgeon	Changes in ECG, troponin or advanced scans
	Respiratory Infection	N	1° Project Officer 2° Surgeon	Changes on chest x-ray in conjunction with clinical findings
	Urinary tract Infection	N	1° Project Officer 2° Surgeon	Positive urine culture with symptoms
	Urinary Retention	N	1° Project Officer 2° Surgeon	> 500mls on bladder scan
	In Hospital Fall	N	1° Project Officer 2° Surgeon	Documented fall in patients notes
	Joint stiffness requiring MUA	Y	1° Surgeon 2° Project Officer	Any patient re-admitted for manipulation under anaesthetic for TKA stiffness
	Re-admission to hospital (all causes)	N	1° Project Officer 2° Surgeon	Any documented re-admission to hospital in first 90 days.
	Return to Theatre (all causes)	Y	1° Surgeon 2° Project Officer	Any documented return to theatre for miscellaneous causes (e.g. retained foreign body, patella facetectomy, extensor mechanism disruption)
	Death (all causes)	Y	1° Surgeon 2° Project Officer	Any death related or unrelated to the TKA
For life of prosthesis	PJI	Y	1° AOANJRR 2° Surgeon	All revision procedures (DAIR & single stage & two stage) for infection inside the knee joint
	Joint Instability	Y	1° AOANJRR 2° Surgeon	As per normal AOANJRR surgical reporting
	Fracture	Y	1° AOANJRR 2° Surgeon	As per normal AOANJRR surgical reporting and associated periprosthetic fracture managed with internal fixation
	Implant Breakage	Y	1° AOANJRR 2° Surgeon	As per normal AOANJRR surgical reporting
	Implant Loosening	Y	1° AOANJRR 2° Surgeon	As per normal AOANJRR surgical reporting
	Lysis	Y	1° AOANJRR 2° Surgeon	As per normal AOANJRR surgical reporting

Appendix 5. Three Month Postoperative Patient Complication Questionnaire

Adverse Event	Question
SSI requiring antibiotics only	Did you have a wound infection requiring antibiotic treatment of any kind?
SSI requiring surgery superficial to joint (e.g. wound dehiscence)	Did you have another surgery on your knee because of infection?
Deep vein thrombosis	Were you diagnosed and treated for a blood clot in your leg, also known as a DVT?
Pulmonary Embolus	Were you diagnosed and treated for a blood clot in your lungs, also known as a pulmonary embolus or PE?
Drug Reaction	
• Anaphylaxis	Did you have an anaphylactic reaction to a medication in the last three months resulting in hospital admission?
• Delirium/Confusion	Did you suffer from confusion or delirium from medications related to your total knee replacement in the last three months?
Cardiovascular Event	Have you suffered a heart attack or stroke in the last three months?
Respiratory Infection	Have you suffered a chest infection or pneumonia in the last 3 months?
Urinary tract Infection	Were you treated for a urinary traction infection (UTI) with antibiotics in the last three months
Urinary Retention	Have you required treatment for acute urinary retention in the last 3 months?
In Hospital Fall	Did you have a fall whilst in hospital requiring acute nursing assistance?
Joint stiffness requiring MUA	Did you require a repeat admission to hospital and anaesthetic due to excessive knee stiffness?
Re-admission to hospital (all causes)	At any point in the last three months did you require a readmission to any at hospital for any reason?
Return to Theatre (all causes)	At any point since your total knee replacement did you have any other surgery for any reason?
Fracture	Have you had any fractures around your knee since your total knee replacement?

Appendix 6 – Safety Reporting Assessment Flowchart

Patient reported complication

Any untoward medical occurrence in a patient which, does not necessarily have to have a causal relationship with the treatment [ICH guidelines]. A complication can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a device, whether or not considered related to this device.

Adverse Event (AE):

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device (IMD)

Adverse Device Event (ADE)

Adverse event related to the use of an investigational medical device

Serious Adverse Event (SAE)

An adverse event that:

1. Led to death

2. Led to serious deterioration in the health of the participant, that either resulted in:

   • a life-threatening illness or injury, or

   • a permanent impairment of a body structure or a body function, or

   • in-patient or prolonged hospitalisation, or

   • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure of a body function

3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Serious Adverse Device Event (SADE):

An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Event (USADE):

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

Significant Safety Issue (SSI):

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Appendix 7 – Safety Reporting Assessment Flowchart (NHMRC)
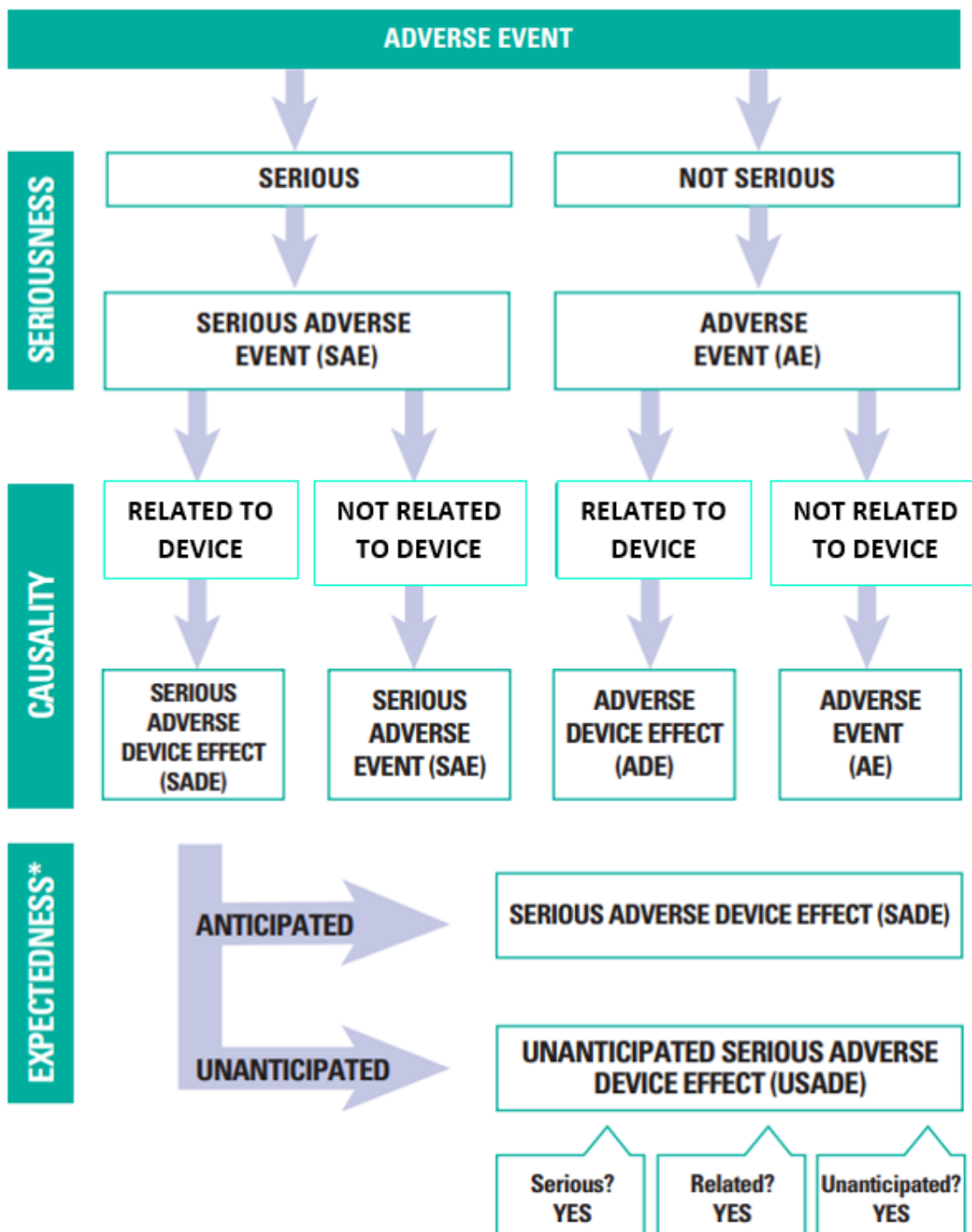
NHMRC Guidance document 'Safety monitoring and reporting in clinical trials involving therapeutic goods'
https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods

22 References

1.   Skou, S.T., et al., *A Randomized, Controlled Trial of Total Knee Replacement.* N Engl J Med, 2015. **373**(17): p. 1597-606.

2.   ACORN, A.C.O.R. *ACORN Annual Report, 2015*. 2015 2015; Available from: http://www.acornregistry.org/images/ACORN_AnnualReport_2015.pdf.

3.   Dunbar, M.J., G. Richardson, and O. Robertsson, *I can't get no satisfaction after my total knee replacement: rhymes and reasons.* Bone Joint J, 2013. **95-b**(11 Suppl A): p. 148-52.

4.   Gunaratne, R., et al., *Patient Dissatisfaction Following Total Knee Arthroplasty: A Systematic Review of the Literature.* J Arthroplasty, 2017. **32**(12): p. 3854-3860.

5.   Wylde, V., et al., *Persistent pain after joint replacement: prevalence, sensory qualities, and postoperative determinants.* PAIN®, 2011. **152**(3): p. 566-572.

6.   Scott, C.E., et al., *Predicting dissatisfaction following total knee arthroplasty in patients under 55 years of age.* Bone Joint J, 2016. **98-B**(12): p. 1625-1634.

7.   Sakellariou, V.I., et al., *Risk Assessment for Chronic Pain and Patient Satisfaction After Total Knee Arthroplasty.* Orthopedics, 2016. **39**(1): p. 55-62.

8.   Nam, D., R.M. Nunley, and R.L. Barrack, *Patient dissatisfaction following total knee replacement: a growing concern?* Bone Joint J, 2014. **96-B**(11 Supple A): p. 96-100.

9.   Ali, A., et al., *Dissatisfied patients after total knee arthroplasty: a registry study involving 114 patients with 8-13 years of followup.* Acta Orthop, 2014. **85**(3): p. 229-33.

10.   Sharkey, P.F., et al., *Why are total knee arthroplasties failing today--has anything changed after 10 years?* J Arthroplasty, 2014. **29**(9): p. 1774-8.

11.   Schroer, W.C., et al., *Why are total knees failing today? Etiology of total knee revision in 2010 and 2011.* J Arthroplasty, 2013. **28**(8 Suppl): p. 116-9.

12.   Lombardi, A.V., Jr., K.R. Berend, and J.B. Adams, *Why knee replacements fail in 2013: patient, surgeon, or implant?* Bone Joint J, 2014. **96-b**(11 Supple A): p. 101-4.

13.   Dalury, D.F., et al., *Why are total knee arthroplasties being revised?* J Arthroplasty, 2013. **28**(8 Suppl): p. 120-1.

14.   Thompson, R., et al., *Arthrofibrosis After Total Knee Arthroplasty: Pathophysiology, Diagnosis, and Management.* Orthop Clin North Am, 2019. **50**(3): p. 269-279.

15.   Mulhall, K.J., et al., *Current etiologies and modes of failure in total knee arthroplasty revision.* Clinical Orthopaedics and Related Research®, 2006. **446**: p. 45-50.

16. Banerjee, S., et al., *Robotic-assisted knee arthroplasty.* Expert Rev Med Devices, 2015. **12**(6): p. 727-35.

17. Lang, J.E., et al., *Robotic systems in orthopaedic surgery.* J Bone Joint Surg Br, 2011. **93**(10): p. 1296-9.

18. Naziri, Q., et al., *The trends in robotic-assisted knee arthroplasty: A statewide database study.* J Orthop, 2019. **16**(3): p. 298-301.

19. Antonios, J.K., et al., *Trends in computer navigation and robotic assistance for total knee arthroplasty in the United States: an analysis of patient and hospital factors.* Arthroplast Today, 2019. **5**(1): p. 88-95.

20. Young, S.W., et al., *The Chitranjan S. Ranawat Award : No Difference in 2-year Functional Outcomes Using Kinematic versus Mechanical Alignment in TKA: A Randomized Controlled Clinical Trial.* Clin Orthop Relat Res, 2017. **475**(1): p. 9-20.

21. Calliess, T., et al., *PSI kinematic versus non-PSI mechanical alignment in total knee arthroplasty: a prospective, randomized study.* Knee Surg Sports Traumatol Arthrosc, 2017. **25**(6): p. 1743-1748.

22. Hutt, J.R., et al., *Kinematic TKA using navigation: Surgical technique and initial results.* Orthop Traumatol Surg Res, 2016. **102**(1): p. 99-104.

23. Dossett, H.G., et al., *A randomised controlled trial of kinematically and mechanically aligned total knee replacements: two-year clinical results.* Bone Joint J, 2014. **96-B**(7): p. 907-13.

24. Howell, S.M., et al., *Accurate alignment and high function after kinematically aligned TKA performed with generic instruments.* Knee Surg Sports Traumatol Arthrosc, 2013. **21**(10): p. 2271-80.

25. Howell, S.M., et al., *Does a kinematically aligned total knee arthroplasty restore function without failure regardless of alignment category?* Clin Orthop Relat Res, 2013. **471**(3): p. 1000-7.

26. Howell, S.M., et al., *Results of an initial experience with custom-fit positioning total knee arthroplasty in a series of 48 patients.* Orthopedics, 2008. **31**(9): p. 857-63.

27. Dossett, H.G., et al., *Kinematically versus mechanically aligned total knee arthroplasty.* Orthopedics, 2012. **35**(2): p. e160-9.

28. Sikorski, J.M., *Alignment in total knee replacement.* J Bone Joint Surg Br, 2008. **90**(9): p. 1121-7.

29.   Aglietti, P. and R. Buzzi, *Posteriorly stabilised total-condylar knee replacement. Three to eight years' follow-up of 85 knees.* J Bone Joint Surg Br, 1988. **70**(2): p. 211-6.

30.   Fang, D.M., M.A. Ritter, and K.E. Davis, *Coronal alignment in total knee arthroplasty: just how important is it?* J Arthroplasty, 2009. **24**(6 Suppl): p. 39-43.

31.   Berend, M.E., et al., *The Chetranjan Ranawat Award: Tibial Component Failure Mechanisms in Total Knee Arthroplasty.* Clinical Orthopaedics and Related Research®, 2004. **428**: p. 26-34.

32.   Ritter, M.A., et al., *Postoperative alignment of total knee replacement. Its effect on survival.* Clin Orthop Relat Res, 1994(299): p. 153-6.

33.   Abdel, M.P. and D.J. Berry, *Current Practice Trends in Primary Hip and Knee Arthroplasties Among Members of the American Association of Hip and Knee Surgeons: A Long-Term Update.* J Arthroplasty, 2019. **34**(7s): p. S24-s27.

34.   Mannan, A., et al., *Increased precision of coronal plane outcomes in robotic-assisted total knee arthroplasty: A systematic review and meta-analysis.* Surgeon, 2018. **16**(4): p. 237-244.

35.   Mason, J.B., et al., *Meta-analysis of alignment outcomes in computer-assisted total knee arthroplasty surgery.* J Arthroplasty, 2007. **22**(8): p. 1097-106.

36.   Hetaimish, B.M., et al., *Meta-analysis of navigation vs conventional total knee arthroplasty.* J Arthroplasty, 2012. **27**(6): p. 1177-82.

37.   de Steiger, R.N., Y.L. Liu, and S.E. Graves, *Computer navigation for total knee arthroplasty reduces revision rate for patients less than sixty-five years of age.* J Bone Joint Surg Am, 2015. **97**(8): p. 635-42.

38.   Liow, M.H., et al., *Robot-assisted total knee arthroplasty accurately restores the joint line and mechanical axis. A prospective randomised study.* J Arthroplasty, 2014. **29**(12): p. 2373-7.

39.   Yim, J.H., et al., *A comparison of classical and anatomical total knee alignment methods in robotic total knee arthroplasty: classical and anatomical knee alignment methods in TKA.* J Arthroplasty, 2013. **28**(6): p. 932-7.

40.   Song, E.K., et al., *Robotic-assisted TKA reduces postoperative alignment outliers and improves gap balance compared to conventional TKA.* Clin Orthop Relat Res, 2013. **471**(1): p. 118-26.

41.   Kim, S.M., et al., *Robot-assisted implantation improves the precision of component position in minimally invasive TKA.* Orthopedics, 2012. **35**(9): p. e1334-9.

42.   Song, E.K., et al., *Simultaneous bilateral total knee arthroplasty with robotic and conventional techniques: a prospective, randomized study.* Knee Surg Sports Traumatol Arthrosc, 2011. **19**(7): p. 1069-76.

43.   Park, S.E. and C.T. Lee, *Comparison of robotic-assisted and conventional manual implantation of a primary total knee arthroplasty.* J Arthroplasty, 2007. **22**(7): p. 1054-9.

44.   Manning, W.A., et al., *A load-measuring device can achieve fine-tuning of mediolateral load at knee arthroplasty but may lead to a more lax knee state.* Knee Surg Sports Traumatol Arthrosc, 2019. **27**(7): p. 2238-2250.

45.   Kayani, B., et al., *Iatrogenic Bone and Soft Tissue Trauma in Robotic-Arm Assisted Total Knee Arthroplasty Compared With Conventional Jig-Based Total Knee Arthroplasty: A Prospective Cohort Study and Validation of a New Classification System.* J Arthroplasty, 2018. **33**(8): p. 2496-2501.

46.   Khlopas, A., et al., *Robotic-Arm Assisted Total Knee Arthroplasty Demonstrated Soft Tissue Protection.* Surg Technol Int, 2017. **30**: p. 441-446.

47.   Sultan, A.A., et al., *Robotic-Arm Assisted Total Knee Arthroplasty More Accurately Restored the Posterior Condylar Offset Ratio and the Insall-Salvati Index Compared to the Manual Technique; A Cohort-Matched Study.* Surg Technol Int, 2019. **34**: p. 409-413.

48.   Marchand, R.C., et al., *One-Year Patient Outcomes for Robotic-Arm-Assisted versus Manual Total Knee Arthroplasty.* J Knee Surg, 2019.

49.   Khlopas, A., et al., *Patient-Reported Functional and Satisfaction Outcomes after Robotic-Arm-Assisted Total Knee Arthroplasty: Early Results of a Prospective Multicenter Investigation.* J Knee Surg, 2019.

50.   Kayani, B., et al., *Robotic-arm assisted total knee arthroplasty has a learning curve of seven cases for integration into the surgical workflow but no learning curve effect for accuracy of implant positioning.* Knee Surg Sports Traumatol Arthrosc, 2019. **27**(4): p. 1132-1141.

51.   Hampp, E.L., et al., *Robotic-Arm Assisted Total Knee Arthroplasty Demonstrated Greater Accuracy and Precision to Plan Compared with Manual Techniques.* J Knee Surg, 2019. **32**(3): p. 239-250.

52.   Sodhi, N., et al., *The Learning Curve Associated with Robotic Total Knee Arthroplasty.* J Knee Surg, 2018. **31**(1): p. 17-21.

53.   Bellemans, J., et al., *The Chitranjan Ranawat award: is neutral mechanical alignment normal for all patients? The concept of constitutional varus.* Clin Orthop Relat Res, 2012. **470**(1): p. 45-53.

54.   Howell, S.M., et al., *Does varus alignment adversely affect implant survival and function six years after kinematically aligned total knee arthroplasty?* Int Orthop, 2015. **39**(11): p. 2117-24.

55.   Delport, H., et al., *Restoration of constitutional alignment in TKA leads to more physiological strains in the collateral ligaments.* Knee Surg Sports Traumatol Arthrosc, 2015. **23**(8): p. 2159-69.

56.   Waterson, H.B., et al., *The early outcome of kinematic versus mechanical alignment in total knee arthroplasty: a prospective randomised control trial.* Bone Joint J, 2016. **98-B**(10): p. 1360-1368.

57.   Thienpont, E., P.E. Schwab, and P. Fennema, *Efficacy of Patient-Specific Instruments in Total Knee Arthroplasty: A Systematic Review and Meta-Analysis.* J Bone Joint Surg Am, 2017. **99**(6): p. 521-530.

58.   Woon, J.T.K., et al., *Outcome of kinematic alignment using patient-specific instrumentation versus mechanical alignment in TKA: a meta-analysis and subgroup analysis of randomised trials.* Arch Orthop Trauma Surg, 2018. **138**(9): p. 1293-1303.

59.   Klasan, A., et al., *Similar Risk of Revision After Kinematically Aligned, Patient-Specific Instrumented Total Knee Arthroplasty, and All Other Total Knee Arthroplasty: Combined Results From the Australian and New Zealand Joint Replacement Registries.* J Arthroplasty, 2020.

60.   Howell, S.M., T.J. Shelton, and M.L. Hull, *Implant Survival and Function Ten Years After Kinematically Aligned Total Knee Arthroplasty.* J Arthroplasty, 2018. **33**(12): p. 3678-3684.

61.   Oussedik, S., et al., *Alignment in total knee arthroplasty.* The Bone & Joint Journal, 2020. **102-B**(3): p. 276-279.

62.   Montgomery, A.A., T.J. Peters, and P. Little, *Design, analysis and presentation of factorial randomised controlled trials.* BMC medical research methodology, 2003. **3**: p. 26-26.

63.   Registry., A.O.A.N.J.R., *Hip, knee & shoulder arthroplasty: annual report 2017. .* https://aoanjrr.sahmri.com/documents/10180/668596/Hip%2C+Knee+%26+Shoulder+Arthroplasty/c287d2a3-22df-a3bb-37a2-91e6c00bfcf0, 2019.

64. Jenny, J.Y. and F. Picard, *Learning navigation - Learning with navigation. A review.* SICOT J, 2017. **3**: p. 39.

65. Hughston, J.C., et al., *Classification of knee ligament instabilities. Part I. The medial compartment and cruciate ligaments.* J Bone Joint Surg Am, 1976. **58**(2): p. 159-72.

66. Hughston, J.C., et al., *Classification of knee ligament instabilities. Part II. The lateral compartment.* J Bone Joint Surg Am, 1976. **58**(2): p. 173-9.

67. Kellgren, J.H. and J.S. Lawrence, *Radiological assessment of osteo-arthrosis.* Ann Rheum Dis, 1957. **16**(4): p. 494-502.

68. Saffarini, M., et al., *The original Akagi line is the most reliable: a systematic review of landmarks for rotational alignment of the tibial component in TKA.* Knee Surg Sports Traumatol Arthrosc, 2019. **27**(4): p. 1018-1027.

69. Akagi, M., et al., *Variability of extraarticular tibial rotation references for total knee arthroplasty.* Clin Orthop Relat Res, 2005(436): p. 172-6.

70. Roos, E.M. *The 2012 User's Guide to: Knee injury and Osteoarthritis Outcome Score (KOOS)*. 2012 [cited 2018 29th April]; Available from: http://www.koos.nu/index.html.

71. *AOA PROMs Pilot Project Final Report*. 2020: https://aoanjrr.sahmri.com/documents/10180/681914/AOANJRR+PROMs+Pilot+Final+Report.

72. Murray, D.W., et al., *The use of the Oxford hip and knee scores.* J Bone Joint Surg Br, 2007. **89**(8): p. 1010-4.

73. Hamilton, D.F., et al., *Validation of the English language Forgotten Joint Score-12 as an outcome measure for total hip and knee arthroplasty in a British population.* Bone Joint J, 2017. **99-b**(2): p. 218-224.

74. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Qual Life Res, 2011. **20**(10): p. 1727-36.

75. EuroQol, G., *EuroQol--a new facility for the measurement of health-related quality of life.* Health Policy, 1990. **16**(3): p. 199-208.

76. Connelly, J.W., et al., *Patient Acceptable Symptom State at 1 and 3 Years After Total Knee Arthroplasty: Thresholds for the Knee Injury and Osteoarthritis Outcome Score (KOOS).* JBJS, 2019. **101**(11): p. 995-1003.

77. Keurentjes, J.C., et al., *Patient acceptable symptom states after totalhip or knee replacement at mid-term follow-up: Thresholds of the Oxford hip and knee scores.* Bone & joint research, 2014. **3**(1): p. 7-13.

78. Gustke, K.A., et al., *Increased satisfaction after total knee replacement using sensor-guided technology.* Bone Joint J, 2014. **96-b**(10): p. 1333-8.

79. Chauhan, S.K., et al., *Computer-assisted total knee replacement. A controlled cadaver study using a multi-parameter quantitative CT assessment of alignment (the Perth CT Protocol).* J Bone Joint Surg Br, 2004. **86**(6): p. 818-23.

80. Naylor, J.M., et al., *Validity and reliability of using photography for measuring knee range of motion: a methodological study.* BMC Musculoskelet Disord, 2011. **12**: p. 77.

81. Podsiadlo, D. and S. Richardson, *The timed "Up & Go": a test of basic functional mobility for frail elderly persons.* J Am Geriatr Soc, 1991. **39**(2): p. 142-8.

82. Ko, V., et al., *The six-minute walk test is an excellent predictor of functional ambulation after total knee arthroplasty.* BMC Musculoskelet Disord, 2013. **14**: p. 145.

83. Mizner, R.L., et al., *Measuring functional improvement after total knee arthroplasty requires both performance-based and patient-report assessments: a longitudinal analysis of outcomes.* J Arthroplasty, 2011. **26**(5): p. 728-37.

84. Petterson, S.C., et al., *Improved function from progressive strengthening interventions after total knee arthroplasty: a randomized clinical trial with an imbedded prospective cohort.* Arthritis Rheum, 2009. **61**(2): p. 174-83.

85. Owens, W.D., J.A. Felts, and E.L. Spitznagel, Jr., *ASA physical status classifications: a study of consistency of ratings.* Anesthesiology, 1978. **49**(4): p. 239-43.

86. Gandek, B., et al., *A 12-item short form of the Knee injury and Osteoarthritis Outcome Score (KOOS-12): tests of reliability, validity and responsiveness.* Osteoarthritis Cartilage, 2019. **27**(5): p. 762-770.

87. Roos, E.M. and S. Toksvig-Larsen, *Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement.* Health Qual Life Outcomes, 2003. **1**: p. 17.