DOES RESTORING THE KINEMATIC ALIGNMENT OF THE KNEE IMPROVE SOFT TISSUE BALANCE DURING TOTAL KNEE ARTHROPLASTY? A RANDOMISED, PARALLEL-GROUP, SUPERIORITY STUDY

Study Protocol

Principal Investigator:

Dr Samuel Macdessi
St George Private Hospital

I have read and agree to follow the
NHMRC National Statement on Ethical Conduct in Research Involving Humans
and confirm that this study will be conducted in accordance with the protocol described herein.

Signature _  **_____. Date __30 March 2018___**

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Roles and Responsibilities -- Contributorship

SM and WG-J conceived of the study. SM, WG-J, and IH initiated the study design and AD, DC and JW assisted with the implementation. WG-J and SG-J designed software to measure x-rays, calculate surgical plan and monitor range of movement. IH provided statistical expertise in clinical trial design, and all authors will assist in primary statistical analysis. All authors contributed to refinement of the study protocol, with SM, IH and JW responsible for the PRO content. All investigators will contribute to development of the manuscript, with SM approving the final manuscript.

Does Restoring the Kinematic Alignment of the Knee Improve Soft Tissue Balance During Total Knee Arthroplasty? A randomised, parallel-group, superiority study

INTRODUCTION

Total knee arthroplasty (TKA) is a successful operation for treating pain and improving mobility in end-stage degenerative arthropathy. Despite advances in implant design and surgical technique, up to 20% of patients are less than satisfied, rating the outcome of their knee arthroplasty as fair or poor [1-3]. Outcomes registries such as the Arthroplasty Clinical Outcomes Registry (ACORN) in Australia [4] and the Swedish Knee Arthroplasty Register [5] report similar rates of dissatisfaction. The causes of this dissatisfaction are not clearly understood but are likely to be multifactorial, with surgical factors such as instability, malalignment, patellofemoral maltracking and stiffness regularly cited as potential contributors. [3, 5-8]

The traditional technique of achieving alignment in TKA is to resect the distal femoral and proximal tibial joint surfaces perpendicular to the long axis of each bone. This is termed the “mechanical alignment” method. External rotation of the femoral resections off the posterior aspect of the femur compensates for the loss of the normal varus alignment of the proximal tibia, leading to parallel cuts with the knee both in extension and flexion. The knee joint is parallel to the floor with the weight bearing axis of the lower limb passing through the middle of the knee joint. These conventional cuts have long been believed to create the best mechanical environment for the function and longevity of the prosthesis.

Advances over recent decades in fixation, manufacturing and improved wear characteristics of the bearing surfaces of total knee prostheses have led to a steady improvement in survivorship of the implants [9]. During this time, however, outcomes have remained consistent, with 15-20% of patients continuing to be dissatisfied with their joint replacement [1-3]. This satisfaction plateau has led some to question the need to focus on creating the ideal mechanical environment for the implant, and instead to suggest ways to accurately recreate the constitutional (or pre-arthritic) alignment of the knee, and thereby achieve improved patient outcomes [10].

In 2012, Bellemans introduced the concept of ‘constitutional varus’ meaning that the proximal tibia is normally in a minor degree of varus alignment, not in neutral mechanical alignment (at right angles to the tibia and femur) and demonstrated the wide range of limb alignment in the normal population [11]. Subsequent to this, the “kinematic alignment” method was developed and first described by Howell et al. The aim of this method is to recreate the constitutional knee joint by recreating the movement around three axes that make up normal knee motion [12]: a transverse axis in the femur about which the tibia flexes and extends; a transverse axis in the femur about which the patella moves; and a longitudinal axis in the tibia about which the tibia internally and externally rotates on the femur. In order to achieve this, the bone

resections are made parallel to the surface of distal femur, posterior femur and proximal tibia, as opposed to perpendicular to the long axis of each bone. The theory is that a knee aligned to the patient's native anatomy will be better balanced (more stable throughout a range of movement), and therefore will require little if any adjustment of the soft tissue envelope to achieve normal knee motion [10].

Despite kinematic alignment gaining increasing traction amongst knee arthroplasty surgeons, there is a lack of clear evidence in the literature supporting claims that a kinematic alignment in total knee arthroplasty optimises knee ligament balance and hence improves patient outcomes.

The feasibility of achieving kinematic alignment with current prostheses and techniques that have been designed to achieve a neutral mechanical axis and a horizontal joint line is not clear. Furthermore, the term *kinematic* implies achievement of complex movement around three independent axes during normal gait. In the absence of dynamic, weight-bearing, 3-dimensional imaging, this intricate action is impossible to assess, and therefore accurate measurement is likely to be currently beyond our grasp. Lastly, the capacity to accurately determine the true joint lines once the arthritic process has occurred is yet to be determined.

New technology allows the surgeon to precisely quantify soft tissue balance in TKA on the operating table, throughout a range of motion [13]. Using these advances, there is evidence that a balanced TKA does, in fact, lead to improved patient outcomes [14].

Notably, however, there has been no work on whether restoring the kinematic alignment of the knee during TKA leads to a more balanced knee than the mechanical alignment method.

What the Evidence Says

To date, there have been four randomised controlled trials looking at the difference between kinematic alignment and mechanical alignment in total knee arthroplasty [15-18], all of which have had significant methodological flaws. All of these studies used patient specific instrumentation (PSI, individually produced cutting guides based on pre-operative imaging) to achieve alignment in the kinematic group. The comparator groups in three of the studies used a combination of intramedullary and extramedullary guides to achieve mechanical alignment [16, 18, 19]. Using different techniques to determine alignment makes comparisons between these techniques difficult. Only one of the studies used the current gold standard of full-optical, computer-assisted navigation [17, 20].

Studies on PSI in the literature have shown it to be no more accurate, and in many cases less accurate, than traditional guides in achieving soft tissue balance; surgeon-led adjustments were required in more than half of cases in some series [21-23]. A recent meta-analysis found that the use of PSI improved femoral alignment and overall limb alignment, but had higher rates of tibial component malalignment when compared to conventional instrumentation [24]. There has been little work comparing the accuracy of PSI to computer-assisted navigation.

There is also significant variation in the definition of *kinematic* in each of these studies. Two of the studies aimed to recreate the original joint line obliquity but neutralise the hip knee ankle angle (HKA) [17, 19]. Only Waterson et al. attempted to correct both the joint line and HKA to the native state [16].

There has been some recent work highlighting the impact of soft tissue balancing on patient satisfaction after TKA. In 2014, Gustke published 2-year follow-up data comparing patient reported outcome measures (PROMs) from a group of TKAs that were balanced with intra-operative pressure sensors and a group that were left unbalanced. The unbalanced group had a satisfaction rate of 82.1%, while 96.7% of those that were accurately balanced were satisfied or very satisfied [14].

To date, there have been no published studies that have compared mechanically aligned TKAs with techniques that aim to recreate the kinematic alignment of the knee using a quantification of balance as the primary outcome measure.

Justification for, and Aims of a New Trial

There has been a recent surge in popularity of kinematic alignment in total knee arthroplasty with a lack of evidence to support the assumed benefits. At the same time, knee ligament balance does appear to be major surgical factor towards an optimised patient outcome. For this reason, a study comparing the balance achieved with methods that restore the kinematic alignment of the knee compared to mechanical alignment is required to guide further research in this area.

The aim of this study is to determine whether ligament balance is more readily achieved by restoring the kinematic alignment versus the traditional method using mechanical alignment. The results of this trial will aim to inform future clinical practice internationally regarding soft tissue balance and kinematic alignment in total knee arthroplasty.

Hypothesis

The hypothesis of this trial is that knees aligned to restore a patient's kinematic (constitutional) alignment will be more objectively balanced compared to those aligned with a neutral mechanical axis and a horizontal joint line.

The differences between these two methods is illustrated below. (Figure 1.)

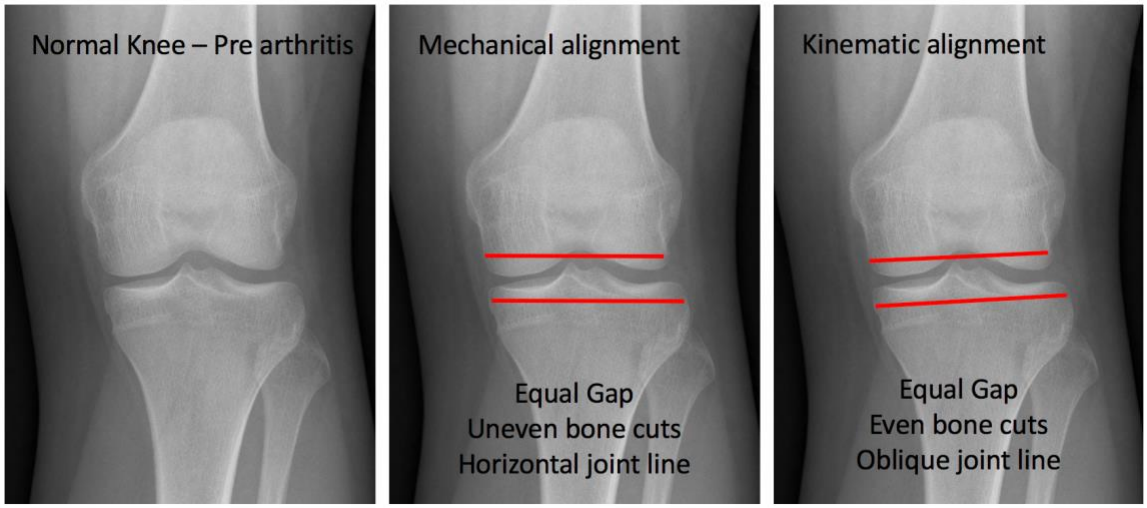


Figure 1. X-ray diagrams of different cuts made during mechanical and kinematic techniques.

METHODS AND ANALYSIS

Study Design

We will conduct a randomised controlled superiority trial (RCT) comparing intra-operative soft tissue balance in TKAs implanted to restore the Kinematic Alignment (KA) as the intervention group versus those aligned by traditional Mechanical Alignment (MA) as the control group.

Unlike previous studies, both groups will be implanted using full optical navigation to improve accuracy. The VERASENSE™ (OrthoSensor, USA) pressure monitoring insert will be used after the proposed alignment has been achieved in both arms of the study, and the initial figures for medial and lateral compartment pressures will be recorded at 10 degrees, 45 degrees and 90 degrees of flexion, as per manufacturer guidance.

Two knee arthroplasty surgeons (SJM, DBC) at one hospital will perform all surgeries. Each surgeon will assess compartmental loads at three positions of knee flexion, verified by navigation data, and these measures will be repeated by the surgical assistant to ensure inter-observer reliability and consistency. The surgical technique described in Appendix 2 and 3. Data will be collected on the frequency and degree of any further adjustments required to satisfactorily balance the knee, as well as the final balance achieved. Although the surgeons will not be blinded to the allocation, the participants, assessors and statisticians will be blinded to enable unbiased collection of patient-reported outcomes and functional outcomes as secondary outcome measures.

To maintain the integrity of the trial, unblinding will occur only when knowledge of the alignment allocation is essential for further clinical management of the patient. Because both treatment arms offer current, routine standards of care, we do not anticipate this need will eventuate. If necessary however, the investigator will contact

the study coordinator to obtain the allocation assignment, and the code break will be reported in the context of Complications documentation.

Inclusion criteria

1. Patients who meet the indications for primary unilateral or bilateral total knee arthroplasty using the Smith & Nephew Legion™ posterior-stabilised total knee arthroplasty system.
2. Patients diagnosed with one or more of the following conditions:
    - Osteoarthritis
    - Rheumatoid inflammatory arthritis
    - Post-traumatic osteoarthritis

Exclusion criteria

1. Revision TKA
2. Previous insufficiency fracture
3. Prior Grade 3 ligamentous knee injury to posterolateral corner (PLC) or lateral collateral ligament (LCL). Grade 3 medial collateral ligament (MCL) injuries treated conservatively may be included so long as they were deemed by the surgeon to have healed with a maximum of Grade 1 laxity.
4. Prior femoral, tibial or patellofemoral osteotomies
5. Ipsilateral foot/ankle or hip arthritis
6. Patients who are unable to provide consent or fulfil the study requirements due to cognitive incapacity or English-language deficiency

During the enrolment period, all patients in the clinical practice of SJM and DBC for whom primary TKA is indicated will be screened for eligibility by the individual surgeon, the clinical investigators and their orthopaedic team. Once patients are found to be eligible for inclusion, they will be invited to participate. Each patient will be given a Patient Information Sheet to educate them on the purpose of the trial, its blinded nature, the confidentiality of their personal information, and requirements for participation. Participants will be given the opportunity to have an informed discussion with an operating surgeon, and their signed informed consent will be obtained prior to randomisation.

ALLOCATION

A 1:1 randomisation scheme will be generated using the computerised program at Randomisation.com (http://www.randomisation.com). To avoid unequal numbers of participants in each group, permutated blocks will be used, with a block size of 4 and 33 blocks allowing for randomisation of a potential 132 subjects.

One hundred thirty-two envelopes will be produced by the study coordinator prior to commencement of the study, each containing a card with the words “Kinematic Alignment” or “Mechanical Alignment” written on it. The opaque envelopes will contain the correct card according to the randomisation plan, and will be sealed and numbered consecutively on the outside. There will be no external information indicating which option is contained on the card within.

Pre-operative planning will be undertaken on each patient for both the intervention and control arms of the study. (See Pre-operative Templating below.) Immediately prior to induction of anaesthesia, a member of the surgical team will open the next envelope in the randomisation sequence from a locked box kept in theatre, and the patient will be allocated to either the intervention or control group.

Bilateral procedures will be included, and randomised once, with both sides being assigned to the same group.

SURGICAL TECHNIQUE

Pre-operative Templating

Prior to the date of surgery, all patients will have weight-bearing, long leg alignment radiographs. These will be taken using the technique described by Paley [25]. Pre-operative Hip Knee Ankle (HKA) angle, Medial Tibial Plateau Angle (MTPA) and Lateral Distal Femoral Angle (LDFA) will be measured for the operative knee using techniques described by Bellemans [11]. A pre-operative plan will then be formulated based on these measurements for re-creation of the coronal plane alignment within a predetermined 'safe zone'.

In order to define the kinematic alignment of each knee, we classified each patients' anatomy based on pre-disease alignment and the obliquity of their joint line using two frequently performed radiographic measurements. A pre-operative plan will then be formulated based on these measurements for re-creation of the coronal plane alignment within a predetermined 'safe zone'.

This 'safe zone' for this study is defined as 86 to 93 degrees for recreation of both the LDFA and the MPTA and -5 degrees to +4 degrees for the HKA. The authors set the parameters of the 'safe zone' centred on the means from Bellemans' paper describing the normal distribution of these angles [11] and also based on studies comparing analysis of alignment against survivorship by Parratte [26] and Ritter [27]. It was felt by the senior knee arthroplasty authors (SJM, DBC) that this safe zone would allow 72% of patients in the KA group to have their constitutional alignment restored according to the data from Bellemans et al., whilst minimising risk of significant component malalignment that would increase the risk of implant failure. It has also been the experience of our group that errors of up to 1 degree commonly occur in individual implant positioning with the use optical navigation. This could result in undesirable alignment errors of up to +/- 5 degrees for implant positioning, and up to +/- 6 degrees for HKA.

The pre-operative plan will involve defining the proximal tibial resection angle and distal femoral resection angles using the LDFA and MPTA measured from the pre-operative films. The resection angle will be set to the nearest whole degree if this falls within the range of 86 to 93 degrees. If it falls outside of this range then it will be set to

either 86 to 93 degrees, depending on which end of the safe zone is closer. If the pre-operative plan requires LDFA and MPTA resections that would lead to a HKA greater than 4 degrees, then the LDFA and MPTA will be adjusted so the total HKA does not exceed the safe zone threshold. In order to reduce the risk of implant subsidence or loosening in the presence of osteoporotic bone, patients with a documented history of osteoporosis requiring bone anti-resorptive therapies, patients with documented insufficiency fractures or patients greater than 80 years of age will have the resection angle range for LFDA and MPTA narrowed to 87 to 93 degrees.

A web-based calculator has been designed to assist with these calculations to reduce any potential error. Most surgical instrumentation, including the navigation system used for this study, measure distal femoral and proximal cuts as either 'varus' or 'valgus'. For the LDFA, 90 degrees is neutral, 86 degrees is 4 degrees of valgus and 93 degrees represents 3 degrees of varus. To avoid errors at the time of surgery, it the varus/valgus figures that correspond to the surgical navigation data that are produced and recorded in the surgical plan. The final surgical plan will be recorded prior to randomisation.

Surgical Technique

Following randomisation, the patients will be allocated to either the intervention group or the control group. All procedures will be performed using optical navigation (OrthoMap Precision Navigation, Stryker, Kalamazoo, MI, USA). The distal femoral and proximal tibial resection will be made as per the allocated group. Femoral component rotation will be set in the KA group parallel to the native posterior condylar axis and in the MA group parallel to the surgical transepicondylar axis. In the KA group, if the planned tibial cut angle has been reduced in order to fall within the safe zone, then the femoral component will be externally rotated by the same amount that the tibial cut was reduced in order to rebalance the flexion gap. A secondary check of flexion gap symmetry will also be undertaken using a gap tensiometer.

Trial components will then be inserted prior to any soft tissue release (other than those required by a standard approach). During trialling, the surgeon will determine the most suitable size of tibial insert, and this will be replaced by a VERASENSE^{TM} insert of the same size. The extensor mechanism will be approximated using a towel clip, and the knee cycled through a full range of movement. Occasionally it may be necessary to change the thickness of the VERASENSE^{TM} insert in response to the pressures being either too high or too low. In this case, the data recordings will be repeated, and the new values will replace those recorded initially. Assessment of knee extension with the computer navigation system will be performed concurrently to ensure that an extension loss of no more than 5 degrees is apparent.

Following this, the surgeon will support the posterior thigh with one hand and rest the heel in the other to reduce the amount of varus and valgus stress placed on the knee (Appendix 1). The knee will then be flexed to 90 degrees (using the optical navigation

to quantify the flexion) and the pressure values captured in this position. This will be repeated at 45 degrees and 10 degrees. The readings will be recorded on the study data collection form by a non-operative member of the surgical team. These steps will be repeated by the surgical assistant, and the data recorded for a second time.

The surgeon will then undertake final balancing of the total knee replacement by standard operating techniques using the Verasense^{TM} insert (Appendices 2 and 3). Any soft tissue or bony adjustments undertaken to achieve this will be recorded on the data collection form. Once knee balancing has been performed, the pressure data will be recorded again.

INTERVENTIONS

Intervention (KA) Group

In the KA group, the surgeon will perform the initial bony resections according to the surgical plan that was defined prior to randomisation. This plan will include an aim for femoral and tibial component position relative to the mechanical axis of the bones. These resections will be guided and validated by the computer navigation system to ensure maximum accuracy. The rest of the procedure will be completed as per the surgical technique described above.

Control (MA) Group

The surgeon will perform the initial bony resections using the same computer navigation system aiming for tibial and femoral component position perpendicular to the mechanical axis of the bone and an overall HKA of 0 degrees. These resections will be validated using the same computer navigation equipment to ensure maximum accuracy. The rest of the procedure will be completed as per the surgical technique described above.

OUTCOME MEASURES

Baseline Measures

Demographics

Baseline demographics will include age at time of surgery, gender, side of surgery, height, weight, body mass index, and primary diagnosis (osteoarthritis, rheumatoid arthritis, post-traumatic osteoarthritis).

Pre-operative Radiographic Data

Radiographic data to be recorded before surgery will include:

1. Hip-knee-ankle (HKA) angle. This is the angle subtended by the mechanical axis of the femur and mechanical axis of the tibia, with a negative value used for varus alignment and positive value for valgus alignment.
2. Lateral distal femoral angle (LDFA). This is the lateral angle subtended by the mechanical axis of the femur and a line across the distal femoral articular surface.
3. Medial proximal tibial angle (MPTA). This is the medial angle subtended by the mechanical axis of the tibia and a line across the proximal tibial articular surface.

Operative Data

Operative data to be recorded will include size of femoral component, size of tibial component, thickness of tibial bearing, size and type (oval, round onlay, inset) of patellar component, total operating time from wound incision to skin closure, intra-operative complications, VERASENSE™ data at 90, 45 and 10 degrees, and any soft tissue or bony adjustments made after the VERASENSE™ recordings.

In-Hospital Data

In-hospital data to be obtained will include total length of stay (from day of surgery to day of discharge), and discharge destination (home, in-patient rehabilitation unit, nursing home facility). Other data to be collected will include blood transfusion requirement (total number of units administered) and other in-hospital complications as specified in Table 2.

Primary Outcome Measure

The primary outcome measure of this study will be the initial difference in pressure between the medial and lateral compartments at 10 degrees of flexion (10-degree pressure delta). Because the compartment pressures will be assessed by both the operating surgeon and an assistant, the mean difference of the two readings will constitute the primary outcome measure.

Secondary Outcome Measures

Knee-Specific Outcome Scores

- *Knee injury and Osteoarthritis Outcome Score (KOOS - www.koos.nu)* - The KOOS score is a patient-administered instrument widely used to assess patients' opinions about their knee pain and function. It consists of five

subscales: Pain, other Symptoms, Activities of Daily Living (ADL), Sport and Recreation (Sport/Rec) and knee-related Quality of Life (QOL). A normalised score is calculated for each subscale, with 100 indicating no symptoms and 0 indicating extreme symptoms. The minimum clinically important change in KOOS has been defined as 8-10 points on a 100-point scale with a reported standard deviation of 16 [28, 29]. We will use the mean of the 3 subscale scores - KOOS Pain, KOOS Symptoms and KOOS ADL with the primary outcome end point will be change in the mean KOOS from pre-operative scores and 12 months. The KOOS at six months, two years, five years and 10 years will also be recorded. We will also analyse each of the five subscale separately as secondary endpoints.

- *Forgotten Joint Score - Knee (FJS-12 Knee - http://www.forgotten-joint-score.info/knee)* - The FJS-12 is a patient-reported tool that was designed to assess patient outcome in patients undergoing conservative or operative treatment of the knee, and focuses on patients' awareness of their knee in everyday life. Joint awareness can be defined as any unintended perception of a joint. This may include strong sensations like pain, but also includes more subtle feelings like mild stiffness, subjective dysfunction, or any discomfort. Generally, joint awareness comes with a negative connotation as healthy joints do not cause 'awareness' in daily life – and are essentially 'forgotten'. The FJS-12 Knee has low ceiling effects, allowing monitoring of longer term outcomes, particularly in well-performing groups after total joint arthroplasty [30]. The FJS-12 will be measured pre-operatively and at one year and two years post-operatively.

Quality of Life Measures

- *EQ5D-5L* (EuroQol Research Foundation, Rotterdam, The Netherlands, *https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/*) is a standard measure of overall health status that provides a simple descriptive profile and a single index value for health status. It describes five health domains: Mobility, Self-Care, Usual Activities, Pain and Discomfort and Depression. A patient indicates his or her current level of health in each of the domains: no problems, slight problems, moderate problems, severe problems or extreme problems. The patient's responses are combined in a 5-digit number describing current health state. Additionally, The EQ VAS records the respondent's self-rated health on a 20-cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents. [29, 30] The EQ5D-5L will be measured pre-operatively and at six months and two years post-operatively.
- *Satisfaction and Success – (http://www.acornregistry.org)* At six months and two years follow-up, patients will be asked questions related to perceived satisfaction and success. The questions are from the Arthroplasty Clinical Outcomes Registry (ACORN), to which the hospitals in this study already contribute. For satisfaction, the question asked is "*How would you describe the results of your operation?*" with five options provided: excellent; very good; good; fair; or poor. For success, the question asked

is *"Overall, how are the problems now with the knee on which you had surgery, compared to before your operation?"* This question also allows the person to choose one of five options: much better; a little better; about the same; a little worse; and much worse [4].

Patient-reported outcomes will be collected prior to clinical assessments, and order of administration will be standardised.

Because the primary outcome measure is recorded intra-operatively, no specific strategy for improving adherence to protocol is necessary, and there is no expected loss to follow-up for that variable.

For the secondary outcome measures, however, strategies for improving adherence to protocol include clear elucidation during the consenting process of the importance of committing to the schedule of follow-up visits, PROMs, and x-rays. Participants will have an opportunity to ask questions, and key messages about the study will be reinforced, at each follow-up visit. In order to prevent missing data and avoid associated complexities in study analysis and interpretation, administrative systems will be employed to diligently schedule follow-up appointments, provide reminders and monitor retention. It is projected that the rate of loss to follow-up for the secondary objectives will be no more than 5%.

Complications

Complications to be recorded will include intra-operative complications, Serious Adverse Events related to the index operation and Adverse Events unrelated to the operation, as defined by the ACORN registry (Table 1). Post-operative complications will be assessed and recorded at all follow-up time points (Table 3), and as necessary at unscheduled times.

Patient-reported outcomes will be monitored throughout the study to supplementally inform the clinical care of individual participants, but their timing coincides with scheduled clinical assessment in any case.

Radiographic Measures

Radiographic investigation will be defined by CT Perth Protocol [31, 32]. This will include HKA Angle, LDFA and MPTA, as well as femoral and tibial component sagittal and rotational position. A routine series of radiographs (AP erect, lateral and skyline views) will also be performed pre-operatively, at six months and two years.

Intra-operative Outcome Measures

Tibiofemoral Compartmental Pressure Loads

- Initial medial and lateral compartmental pressure and final medial and lateral pressure loads will be

compared in both groups at 10º, 45º and 90º of knee flexion. Optimal knee balance will be defined as a pressure difference of less than 15 lb between compartments at 10º, 45º and 90º of knee flexion, with no pressure exceeding 40 lbs.

Functional Outcome Measures

Knee Range of Motion – The patient's range of motion will be measured by a blinded orthopaedic nurse at two weeks, eight to twelve weeks and one year post-operatively. Two photographs will be taken with the patient in the supine position with markers placed on the greater trochanter, lateral epicondyle of the femur and lateral malleolus. One photograph will be taken in maximal active extension and one in maximal active flexion, with the nurse standing between 1 and 1.2m from the table to get the entire lower limb in full view and holding the camera lens level with and parallel to the patient's knee. Measurements from the photographs will be taken using computer angle measurement software. Knee flexion will be recorded as a positive value and knee hyperextension as a negative value. The following will be recorded: maximal active extension (with hyperextension as negative, full extension as zero and flexion contracture as positive); and maximal active flexion. From these two values, the arc of knee motion will be recorded (flexion minus extension).

SAMPLE SIZE

The senior authors have previously recorded the initial and final intra-compartment pressures of 280 consecutive TKAs using the VERASENSE™ device. The mean initial 10-degree pressure difference was 30psi (SD 30psi). The manufacturers recommend a pressure difference between lateral and medial compartments of <15psi in order for the knee to be balanced. Using a 5% significance, a standard deviation of 30 and an 80% power to detect a difference of 15psi, a sample size of 125 will be required. As the primary outcome measure is an intraoperative measurement, loss to follow-up will not be significant.

In addition, we aim to determine whether any differences exist in patient reported outcomes in balanced TKA's inserted with the KA or MA method. Roos and colleagues in 2003 reported a change in KOOS Pain, KOOS Symptoms and KOOS Function of 45, 37 and 41 a cohort of patients undergoing TKA [28]. The minimal clinically important change in KOOS was between 8 and 10, with a standard deviation of 16. Using a one-to-one allocation, 5% significance and 80% power to detect a 8 point change on KOOS score, a sample size of approximately 64 patients per group will be required, which would approximate the sample size of our study. [Table 2].

DATA COLLECTION AND MONITORING

The primary outcome measure (initial pressure delta between medial and lateral compartments at 10 degrees of flexion) will be recorded intra-operatively by operating room staff in a locked and password-protected spreadsheet. The surgeon and assistant surgeon will each confirm the recorded measurement at the end of each case, and longitudinal checks for consistency and validity will be employed throughout the study.

All PROM data will be obtained from patients at pre-operative and post-operative consultations in paper form, and then stored centrally in a locked and password-protected electronic database (Socrates). Intra-operative data will be collected by members of the surgical team. In-hospital data will be collected by the trial co-ordinator. A CT radiographer with experience in performing post-operative alignment measures will be blinded to patient allocation, and will perform all CT-based radiographic measures.

No formal data monitoring committee is deemed necessary for this trial because of its minimal risks and because both trial arms offer standard, accepted surgical interventions. The accumulating data, however, will be monitored continuously by the principal investigator and the study monitor to determine if the trial should be modified or discontinued.

Auditing of trial conduct, including site monitoring visits, will be carried out independently by the Bellberry Limited Human Research Ethics Committee.

Stopping Rules

The trial will be terminated early if there are two (2) or more cases of tibiofemoral knee joint instability, patellofemoral instability or implant subsidence or loosening in patients assigned to the intervention arm within two years post-operatively, or if monitoring indicates a pattern of unexpected serious adverse events.

DATA ANALYSIS

The primary outcome for this study will be soft tissue balance, defined as the mean of the initial difference in pressure between the medial and lateral compartments at 10 degrees of flexion (10-degree pressure delta) measured by both the surgeon and the assistant intra-operatively immediately after the bone cuts and prior to any soft tissue correction.

Normality of data distribution will be assessed and the Student's t-test will be used to compare differences in means with continuous variables. The Chi-squared test and Fishers exact test will be used for categorical data analysis as appropriate. Intention-to-treat analysis will be performed in the primary analysis. In addition, a per-protocol analysis including participants according to treatment received will also be added as a secondary analysis. Analysis of secondary outcomes will include mixed-model

analyses comparing secondary outcomes between time points. If greater than 20% of data is missing from the randomised sample, the missing data will be imputed. However, attempts will be made to minimise missing data by contacting patients directly by phone or via mail follow-up.

ETHICS AND DISSEMINATION

Safety considerations

Because the two groups being analysed will both be offered current routine standards of care, we do not anticipate that either the intervention or control arm will be associated with any adverse events beyond those to which patients are normally exposed during total knee arthroplasty surgery.

The trial will be conducted at St George Private Hospital (Kogarah, NSW) which has provisions for liability insurance. There will be specific information included in the Patient Information Sheet and Consent form instructing the participant to notify the principal investigators of any adverse events or complications that arise during the course of the trial.

Ethics

This study protocol was approved by the ethics committee of Bellberry Limited on 16 January 2018 (#2017-12-911) and was registered with the Australian New Zealand Clinical Trials Registry (#ACTRN12617001627347p).

Important modifications to the protocol that may impact the conduct of the study (including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects) will be communicated to Bellberry Limited and the St George Private Hospital governance board as necessary for their approval. Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted.

The investigators believe that conducting a randomised trial to determine if restoring the native kinematic alignment of the knee improves the soft tissue balance achieved during total knee arthroplasty is an ethical way to undertake such a study, as the potential benefits to society will outweigh the potential risks to the individuals involved. As both groups are receiving an accepted standard of care for knee surgical balance, we see no significant risks to the patient that will be outside the norm for patients undergoing total knee arthroplasty surgery.

None of the participants in this study will be paid. None of the investigators has any financial or other conflicts of interest in the process or outcomes of this trial.

Participants are clearly instructed in the Patient Information and Consent Form to contact the treating doctor as soon as possible if they suffer any injuries or complications they believe are related to the trial, and they are informed about their legal rights to compensation for any serious harm resulting from participation. They are also assured verbally and via the Patient Information and Consent Form that their clinical follow-up will continue on a regular basis after the conclusion of this study.

Funding

The equipment used in this study is part of the routine practice of the senior authors, as is the data collection required for the outcome measures. As such, this study will require no additional funding from external sponsors.

Data Management

All records that contain names or other personal identifiers (such as consent forms) will be stored separately from study records identified by code numbers. Study data will be stored in the Socrates (Standardised Orthopaedic Clinical Research and Treatment Evaluation Software, Ortholink, NSW) research database by the research co-ordinator. The data will be protected on a password-protected computer and any papers will be locked in a filing cabinet accessible only to the principal investigator and the co-ordinator. At the end of the study period, all paper copies will be scanned and destroyed.

During the trial period, the principal investigator and study coordinator will have access to the full trial data set.

Dissemination

The aggregate, de-identified results of this research will be presented at both national and international orthopaedic surgical meetings such as the Australian Orthopaedic Association Annual Scientific Meeting, the Australian Knee Society Meeting, and the American Academy of Orthopaedic Surgeons. We aim to have this research submitted to a high-impact medical or surgical journal for publication, and all investigators are eligible for authorship in such publications.

It is also anticipated that the results of this trial will inform future research efforts, clinical practice and surgical guidelines internationally. To that end, and to enhance transparency, reproducibility and interpretation of the study results, this protocol will be made publicly available via open-access digital publication. Additionally, the authors will publish a de-identified, participant-level data set and statistical code after journal publication to enable verification and replication of the study.

TABLES

Table 1. Adverse Events (as per ACORN Protocol)

- Drug Reaction
- Delirium
- SSI requiring oral antibiotics
- SSI requiring IV antibiotics
- SSI requiring surgery without prosthetic removal
- SSI requiring surgery with prosthetic removal
- Deep venous thrombosis
- Pulmonary Embolus
- Fat Emboli
- Respiratory Infection
- CVS
- Dislocation
- Fracture
- Nerve Injury
- Urinary Tract Infection
- Urinary Retention
- Wound Dehiscence
- Reoperation During Index Admission
- Pressure Area
- Fall
- Hypotension
- Cellulitis
- Death
- Other

Table 2. Sample Size Calculation

Parameters	Results
Power	80%
Alpha	0.05
Mean (Group 1)	30
Mean (Group 2)	15
Standard deviation	30
Sample size	**125**
Power (obtained)	1

Table 3. Schedule of Study Assessments

	Pre-op	Intra-op	On discharge	2 weeks	6-8 weeks	6 months	1 year	2 years
Written informed consent	X							
Demographics	X							
VERASENSE™ Data		X	X					
KOOS	X					X	X	X
FJS	X						X	X
EQ5D-5L, Satisfaction	X					X		X
Knee Range of Motion	X			X	X	X		
Radiographs	X		X			X		X
CT Perth Protocol			X					
Adverse Event Reporting		X	X	X	X	X	X	X

Table 4. SPIRIT 2013 Checklist with SPIRIT-PRO Extensions

SPIRIT 2013 Checklist with SPIRIT-PRO Extensions				
SPIRIT Section	**Item No.**	**Item Description**	**SPIRIT-Pro Extension**	**Addressed on Page No.**
Administrative Information				
Title	1	Descriptive title identifying study design, population, interventions, and if applicable, trial acronym		Title page
Trial registration	2a	Trial identifier and registry name (if not yet registered, name of intended registry)		19
	2b	All items from the World Health Organization Trial Registration Data Set		N/A
Protocol version	3	Date and version identifier		Footer
Funding	4	Sources and types of financial, material and other support		19
Roles and responsibilities	5a	Names, affiliations and roles of protocol contributors		4-5
	5b	Name and contact information for trial sponsor		19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities		N/A
	5d	Composition, roles and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team and other individuals or groups overseeing the trial, if applicable		N/A
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Description of the PRO-specific research question and rationale for PRO assessment. Summary of PRO findings in relevant studies	6-8 14-15
	6b	Explanation for choice of comparators		8
Objectives	7	Specific objectives or hypotheses	Statement of PRO objectives or hypotheses (including relevant PRO concepts/domains)	8 14-15
Trial design	8	Description of trial design, including type of trial (e.g. parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g. superiority, equivalence, non-inferiority, exploratory)		9-10
Methods: Participants, Interventions and Outcomes				
Study setting	9	Description of study settings (e.g. community clinic, academic hospital) and list of countries where data will be collected; reference to where list of study sites can be obtained		19
Eligibility criteria	10	Inclusion and exclusion criteria for participants; if applicable, eligibility for study centres and individuals who will perform the interventions (e.g. surgeons, psychotherapists)	Specify any PRO-specific eligibility criteria (e.g. language/reading requirements or pre-randomisation completion of PRO). If PROs will not be collect from the entire sample, provide rationale and describe the method for obtaining the PRO sub-sample.	10
Interventions	11a	Interventions for each group with sufficient data detail to allow replication, including how and when they will be administered		11-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g. drug dose change in response to harms, participant request, or improving/worsening disease). (Stopping rules)		18

SPIRIT 2013 Checklist with SPIRIT-PRO Extensions				
SPIRIT Section	**Item No.**	**Item Description**	**SPIRIT-Pro Extension**	**Addressed on Page No.**
	11c	Strategies to improve adherence to intervention protocols and any procedures for monitoring adherence (e.g. durg tablet return, laboratory tests)		16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial		N/A
Outcomes	12	Primary, secondary and other outcomes, including the specific measurement variable (e.g. systolic blood pressure), analysis metric (e.g. change from baseline, final value, time to event), method of aggregation (e.g. median, proportion), and time point for each outcome	Specification of the PRO concepts/domains used to evaluate the intervention (e.g. overall health-related quality of life, specific domain, specific symptom) and for each one, the analysis metric (e.g. change from baseline, final value, time to event) and the principal time point or period of interest	13-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments and visits for participants; a schematic diagram is highly recommended	Inclusion of a schedule of PRO assessments, providing a rationale for the time points and justifying if the initial assessment is not pre-randomisation. Specification of time windows, whether PRO collection is prior to clinical assessments and if using multiple questionnaires, whether order of administration will be standardised.	14-17 22
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumption supporting any sample size calculations	When a PRO is the primary end point, statement of the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size		10
Methods: Assignment of Interventions (for Clinical Trials)				
Allocation Sequence generation	16a	Method of generating the allocation sequence (e.g. computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g. blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.		10-11
Concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g. central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned		11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions		11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g. trial participants, care providers, outcome assessors, data analysts) and how		9
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial		10
Methods: Data Collection, Management and Analysis				
Data Collection Methods	18a	Plans for assessment and collection of outcome, baseline and other trial data, including any related processes to promote data quality (e.g. duplicate measurements, training of assessors) and description	Justification of the PRO instrument to be used and description of domains, number of items, recall period	13-17

SPIRIT Section	Item No.	Item Description	SPIRIT-Pro Extension	Addressed on Page No.
		of study instruments (e.g. questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	and instrument scaling and scoring (e.g. range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines and patient acceptability and burden if available, ideally in the population of interest. Statement of whether the measure will be used in accordance with any user manual, and specification and justification of deviations if planned.	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Specification of PRO data collection management strategies for minimising avoidable missing data. Description of process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	16
Data management	19	Plans for data entry, coding, security and storage, including any related processes to promote data quality (e.g. double data entry, range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol		20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol		18
	20b	Methods for any additional analyses (e.g. subgroup and adjusted analyses)		N/A
	20c	Definition of analysis population relating to protocol non-adherence (e.g. as randomised analysis) and any statistical methods to handle missing data (e.g. multiple imputation)		18
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a data monitoring committee is not needed		18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		18
Harms	22	Plans for collecting, assessing, reporting and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants, and if so, how this will be managed in a standardised way. Describe how this process will be explained to participants (e.g. in the Participant Information Sheet and Consent Form)	16, 19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and sponsor(s).		18
Ethics and Dissemination				

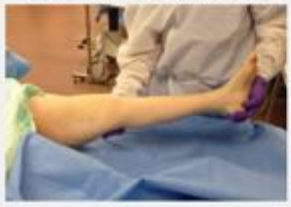
SPIRIT 2013 Checklist with SPIRIT-PRO Extensions

SPIRIT Section	Item No.	Item Description	SPIRIT-Pro Extension	Addressed on Page No.
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board approval		19
Protocol amendments	25	Plans for communicating important protocol modifications (e.g. changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g investigators, research ethics committees/institutional review boards, trial participants, trial registries, journals, regulators)		19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates and how (see item 32)		10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared and maintained to protect confidentiality before, during and after the trial		10, 19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site		19
Access to data	29	Statement of who will have access to the final trial data set and disclosure of contractual agreements that limit such access for investigators		20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who are harmed by trial participation		19
Dissemination policy Trial results	31a	Plans for investigators and sponsor(s) to communicate trial results to participants, health care professionals, the public and other relevant groups (e.g. via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions		20
Authorship	31b	Authorship eligibility guidelines and any intended use of professional writers		20
Reproducible research	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code		20
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates		Appendix 5
Biological specimens	33	Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable		N/A

APPENDICES

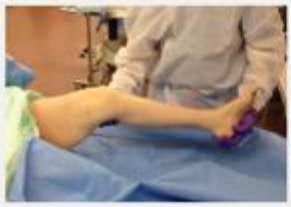
Appendix 1. Leg Positioning for VERASENSE™ Pressure Calculations

HOLDING THE LEG For the correct depiction of intra-articular loading, in extension and flexion, the leg must be held with posterior support:



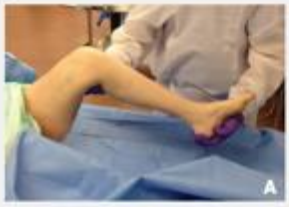
Step 1.

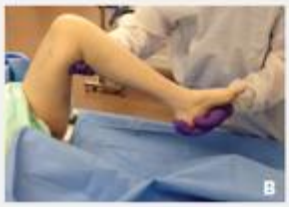
With the leg in extension, one hand is placed on the heel of the operative leg; one hand is placed under the backside of the knee, at the posterior capsule.



Step 2.

Initial evaluation of soft tissue should always be assessed with the leg flexed in 10° with the posterior capsule relaxed and the screw home mechanism disengaged. Failure to do so could result in the over-releasing of soft-tissue, as loads tend to increase during terminal extension due to the screw home mechanism.

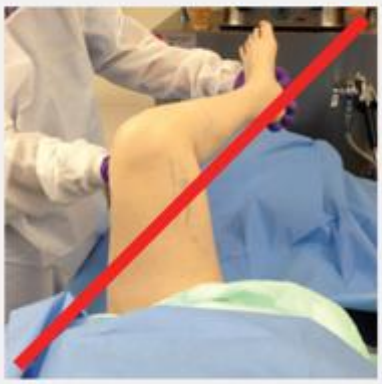




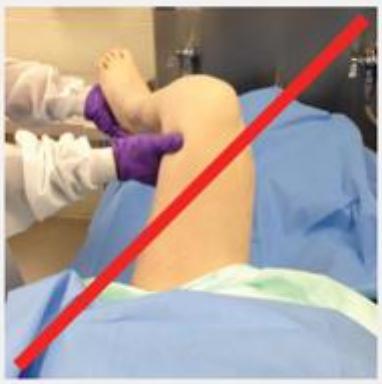
Step 3.

Soft tissues should continue to be evaluated at 45° (FIG A) and 90° of flexion (FIG B). If using a cruciate retaining component, an intraoperative posterior drawer test will allow the surgeon to assess PCL stability using the VERASENSE tracking option (FIG C).

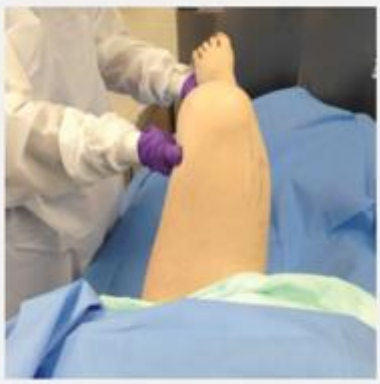
HOLDING THE LEG (CONTINUED)



INCORRECT
Abducted/Externally Rotated



INCORRECT
Adducted/Internally Rotated



CORRECT
Neutral Position

Appendix 2. Balancing of the Varus Knee

SURGICAL TECHNIQUE QUICK REFERENCE

Authored By: Martin W. Roche, M.D.
Holy Cross Hospital, Fort Lauderdale, FL
Patrick A. Meere, M.D.
NYU Langone Medical Center, New York, NY

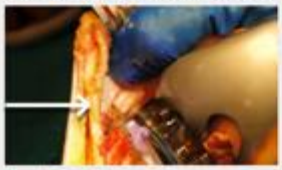
Assess soft-tissue load references with **joint reduced and capsule closed**. Only address soft-tissues after loads have been assessed in both **extension and flexion (10°-90°)**. After any tissue release, the **leg should be "cycled"** (taken through the range of motion) several times.

APPROACH TO VARUS KNEE

TIGHT IN EXTENSION - MEDIALLY

SENSOR PRESENTATION:

SURGICAL CONSIDERATION:



Evaluate MCL

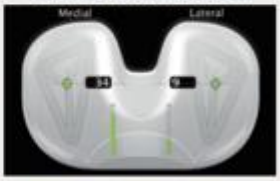
Palpate fibers of MCL to assess tension. Release **posterior fibers of MCL** (both deep and superficial).

Evaluate Medial Posterior Capsule

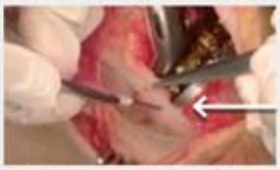
Release medial posterior capsule and/or semimembranousus at tibial attachment site.

TIGHT IN FLEXION - MEDIALLY

SENSOR PRESENTATION:



SURGICAL CONSIDERATION:



Condition 1. **Evaluate MCL**

Palpate fibers of MCL to assess tension. Release **anterior fibers of MCL** (both deep and superficial).

SENSOR PRESENTATION:

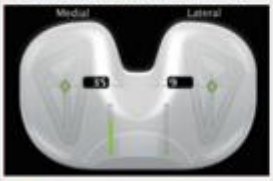
SURGICAL CONSIDERATION:

Condition 2. **Evaluate PCL**

If medial femoral contact point exhibits excessive tension and posterior positioning, release **anterolateral bundle PCL fibers**.

TIGHT IN FLEXION AND EXTENSION - MEDIALLY

SENSOR PRESENTATION:



SURGICAL CONSIDERATION:

Condition 1. **Loads 20-40 lbs.**

Extension Balancing:

- Posterior MCL fibers released if in tension; loads rechecked.
- Posterior medial capsule checked for tension and released, if needed; loads re-checked.
- If necessary, semimembranosus can be released.

Flexion Balancing:

- Anterior MCL fibers released if in tension; loads rechecked.

SENSOR PRESENTATION:

SURGICAL CONSIDERATION:

Condition 2. **Loads > 40 lbs.**

If loads beyond 40 lbs. are displayed, consider recutting the tibia plateau **to add additional varus** alignment.

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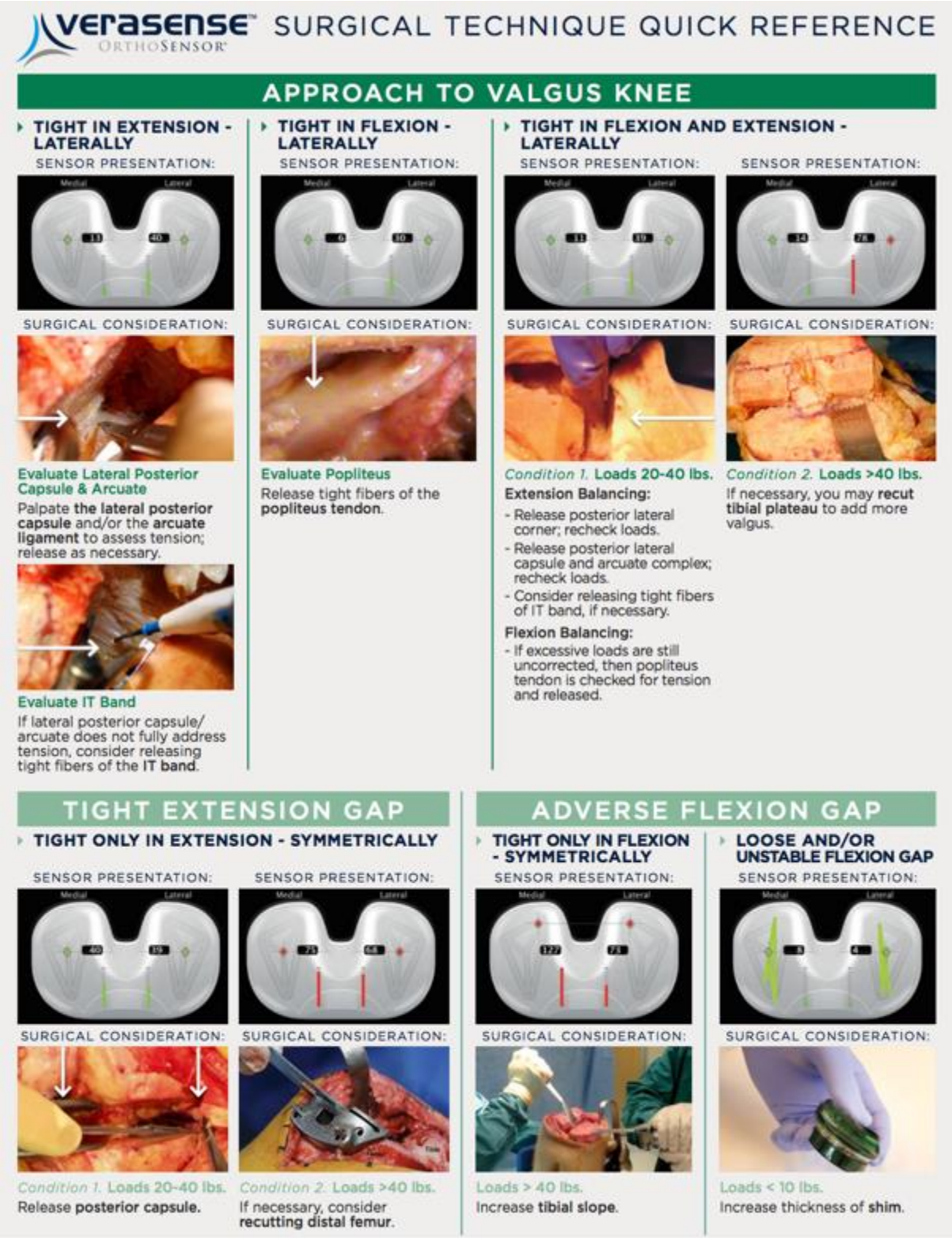
Training and Education Training@OrthoSensor.com

Appendix 3. Balancing of the Valgus Knee



Appendix 4. Participant Information Sheet and Consent Form

See link at Sydney Knee Specialists website: http://www.sydneyknee.com.au/.

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