CONFIDENTIAL

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A prospective, randomised controlled trial evaluating Total Knee Replacement with the Stryker Triathlon Primary Total Knee System performed using Stryker's Robotic-arm assisted surgery system, Mako, compared to Bicompartmental Knee Replacement with Restoris MCK Multicompartmental Knee System performed using Stryker's Robotic-arm assisted surgery system, Mako

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I have read and agree to follow the NHMRC National Statement on Ethical Conduct in Research Involving Humans.

Signature _____ Date_____

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1.0 SUMMARY

This study is a prospective, randomised clinical study comparing clinical outcomes of Knee Replacement using the Oxford Knee Score (OKS), in patients receiving either Bicompartmental Knee Replacement or Total Knee Replacement performed using Stryker's robotic-arm assisted surgery system Mako, Functional and radiographic outcomes will be additionally collected as part of this study.

The study will be conducted in patients with non-inflammatory degenerative joint disease who are randomised to either the Restoris® MCK Multicompartmental Knee System for Bicompartmental Knee Replacement (BKR), or the Triathlon Total Knee System for Total Knee Replacement (TKR), with a minimum 2 year patient evaluation period.

All components used in this study are TGA approved, listed on the Australian Register of Therapeutic Goods. This study will be a phase IV post-market clinical trial.

A minimum cohort of **70** patients will be enrolled into the study in Australia.

Patients who are eligible for knee replacement surgery and meet the inclusion/exclusion criteria, will be enrolled into the study and randomised to receive either the Restoris® MCK Multicompartmental Knee System or Triathlon Primary Total Knee System. Patients will undergo a series of evaluations both pre-operatively, intra-operatively and post-operatively, in accordance with the below schedule:

PATIENT EVALUATON SCHEDULE

EVALUATION	History/ Pre-Op	Intra-Op	Post op ≤5 days after surgery	6 week follow-up (± 2 weeks)	3 month follow-up (± 2 weeks)	12 month follow-up (± 1 month)	24 month follow-up (± 2 months)
Date of Visit	✓	✓	✓	✓	✓	✓	✓
Pre Op Clinical Data	✓						
Inclusion / Exclusion Criteria	✓						
Randomisation	✓						
Surgical Details (All surgery, Bicompartmental Surgery, Total Knee Replacement)		✓					
Oxford Knee Score	✓			✓	✓	✓	✓
EQ-5D	✓				✓	✓	✓
VAS Pain	✓				✓	✓	✓
New Knee Society Score	✓				✓		✓
Forgotten Joint Score	✓				✓	✓	✓
Length of Stay				✓			
MAKO CT or MAKO CT Arthrogram	✓**						
Anteroposterior (A/P) and Lateral Knee Radiographs	✓		✓*		✓	✓	✓
Skyline Knee radiographs	✓					✓	✓
Adverse Events		✓	✓	✓	✓	✓	✓
Serious Adverse Events	✓	✓	✓	✓	✓	✓	✓
Protocol Deviations	✓	✓	✓	✓	✓	✓	✓

*A/P and Lateral Knee Radiographs collected post op ≤5 days after surgery are non-weight bearing

** MAKO CT Arthrogram to be performed if the patient has not had a previous MRI or MRI/CT Arthrogram. MAKO CT to be performed if the patient has had a previous MRI or MRI/CT Arthrogram.

Please refer to Section 11.0 Evaluations: Radiographs for the coverage specifications of each radiograph listed in the patient evaluation schedule.

2.0 INTRODUCTION

The number of Total Knee Replacement procedures is increasing due to an older demographic and a heavier population group. Individuals have higher expectations of their knee replacement surgery and function due to an increasing participation in sporting activities. As newer technologies are developing, the use of evidence based medicine is critically important (Walker at al. 2009).

The 2014 Australian National Joint Registry Annual Report states 41 250 patients underwent Unicompartmental Knee Replacement (UKR), 165 patients underwent Bicompartmental Knee Replacement (BKR) and 396 472 patients underwent Total Knee Replacement (TKR), with TKR figures increasing by more than 44 500 procedures from the previous 2013 report (AOANJRR).

In 2011 the Triathlon Total Knee System was the third most implanted prosthesis in England and Wales. In Australia it has been the most implanted prosthesis for Primary Total Knee Replacement since 2009 as reported by the National Joint Registry. Five year results report good midterm survivorship along with functional outcomes and patient satisfaction. (Scott et al. 2014)

Unicompartmental Knee Replacement and Patellofemoral replacement have both shown improved function and faster recovery times postoperatively. Interest in Bicompartmental

Knee Replacement is increasing as innovation improves results, resulting in higher patient function levels (Argenson et al. 2009).

Currently there are a limited number of studies that report on Bicompartmental Knee Replacement outcomes, and even fewer prospective Randomised Control Trials (RCT) reported on this method. It has been idealised that Bicompartmental Knee Replacement may provide better function when compared to Total Knee Replacement, however additional studies are required (Engh et al. 2014).

Surgical accuracy in Total Knee Replacement has previously been improved by using computer assisted surgical navigation. New robotic arm technology has been developed to constrain the motion of the cutting tool used by the surgeon. The robotic arm remains under direct control of the surgeon, and the surgeon has the ability to dictate the movement constraints to increase reproducibility, accuracy and precision (Conditt et al. 2009)

Stryker's robotic arm assisted surgery offers treatment to patients who do not have osteoarthritis in all three compartments of the knee. A 3-D plan is created from the patients CT scan to provide implant size, placement and alignment. The robotic arm is controlled by the surgeon, and benefits of this technology include a smaller incision, live feedback, bone sparing capabilities and a shorter length of stay in hospital (Makoplasty)

This study will assess Bicompartmental Knee Replacement using Restoris MCK Multicompartmental Knee System, to Total Knee Replacement using Stryker's Primary Triathlon Total Knee System. Both surgeries will be conducted using Stryker robotic arm assisted surgery system (MAKO). Clinical and functional outcomes will be assessed between the two groups using the Oxford Knee Score as the primary endpoint. Radiographic outcomes will be collected to measure pre-operative cartilage wear, and any incidences of loosening and revision.

As all components used in this study are TGA approved, this will be a phase IV, post-market study.

3.0 OBJECTIVES

PRIMARY

The primary objective of this study is:

- To compare the clinical outcomes of Knee Replacement surgery using the Oxford Knee Score (OKS) at 24 months, in patients receiving Bicompartmental Knee Replacement using Restoris MCK Multicompartmental Knee System with Stryker's robotic-arm assisted surgery system Mako, to Total Knee Replacement using the Triathlon Total Knee System performed with Stryker's robotic-arm assisted surgery system Mako.

SECONDARY

The secondary objectives of this study are:

- To determine functional and clinical outcomes of Bicompartmental Knee Replacement (BKR) and Total Knee Replacement (TKR) (including pain, function and health-related quality of life) with Restoris MCK Multicompartmental Knee System and Triathlon Primary Total Knee System at 24 months via:
    - EQ-5D: The EQ-5D is a standardised instrument for use as a measure of health outcome.
    - VAS Pain: A graphical Visual Analog Scale that patients use to indicate their level of pain.
    - New Knee Society Score 2011 (KSS): A validated score assessing surgeon generated objective measures based on technical outcomes, and subjective measures based on patient satisfaction, patient expectations and functional activity of the knee (Noble et al. 2012) (Scuderi et al. 2012).
    - Forgotten Joint Score (FJS): The Forgotten Joint Score is a newly-developed twelve-item, self-reported assessment of how aware recipients

of hip and knee joint replacement are of their joint in everyday life (Behrend et al, 2011).

- To compare incidence of loosening, reoperation and revision in patients receiving Restoris MCK Multicompartmental Knee System, compared to Triathlon Total Knee System.
- To determine length of hospital stay in patients receiving Restoris MCK Multicompartmental Knee System, compared to Triathlon Total Knee System.

4.0 NUMBER OF PATIENTS

This study will enrol a total of **70 cases**, of which 35 will be randomised to receive the Restoris MCK Multicompartmental Knee System and 35 will be randomised to receive the Triathlon Primary Total Knee System. See section 12.2 for sample size justification.

Additional patients will be recruited to compensate for early withdrawals and terminations.

5.0 LENGTH OF STUDY

Individual study patients will be followed up for a period of 2 years after surgery.

The enrolment period is expected to be 6-9 months or until the required sample size is reached; it is therefore anticipated that the entire study will take a further 33 months (minimum) to complete.

6.0 PATIENT SELECTION CRITERIA

The Investigator is responsible for evaluating each patient against the following criteria and assuring that the patient meets the requirements to be enrolled in this clinical investigation. Each patient enrolled in this investigation must meet each of the following inclusion criteria and have none of the exclusion criteria. The Investigator must notify the Ethics Committee of any patient enrolled in this study who does not meet the inclusion

and exclusion criteria. Inclusion/Exclusion criteria have been limited to reflect the actual patient population for this post-market assessment.

Investigators are also expected to follow the instructions for use of all devices involved in this study, in accordance with their usual clinical practice.

6.1 Inclusion Criteria

1. The patient is a suitable candidate for a Bicompartmental Knee Replacement and has moderate to severe patellofemoral wear and medial compartment wear (surgeons discretion)
2. The patient has no fixed flexion greater than 10 degrees.
3. The patient has maximal flexion greater than 100 degrees
4. The patient has a passively correctable varus deformity
5. The patient has a functionally Intact ACL.
6. The patient has no significant patellofemoral malalignment
7. The patient has negligible lateral compartment degeneration with no appreciable loss of cartilage height (surgeon's discretion).
8. The patient has pain that is not localised to the medial compartment only
9. The patient is a male or non-pregnant female.
10. The patient has signed the study specific, HREC-approved, Informed Consent document and is willing and able to comply with the specified pre-operative and post-operative clinical and radiographic evaluations.

6.2 Exclusion Criteria

1. The patient has a clinically deficient ACL and cruciate and collateral ligament insufficiency on MRI or MRI/CT Arthrogram.
2. The patient is undergoing revision surgery
3. The patient has greater than 10° of hyperextension, greater than 10° of varus or valgus deformity, greater than 10° Flexion Contracture
4. The patient has active, local infection or previous intra-articular infection
5. The patient has skeletal immaturity
6. The patient is without sufficient bone stock to allow appropriate insertion and fixation of the prosthesis

7. The patient's weight, age or activity level might cause extreme loads and early failure of the system (surgeons discretion).
8. The patient has a systemic or local condition that would limit the ability to assess the performance of the device e.g. neuromuscular or neurosensory deficiency, disorder leading to progressive bone deterioration (including rheumatoid arthritis and osteoporosis), or patient is immunologically suppressed.
9. Patient has a cognitive impairment, an intellectual disability or a mental illness that is considered by the investigator to inhibit the patient's capacity to consent to research and the ability to participate in it
10. Patients with tricompartmental disease are contraindicated from the study

7.0 STUDY DESIGN

This is a prospective, randomised, study with patients treated at multiple hospitals.

Prior to each surgeon enrolling their first study patient, they must be accredited to perform Stryker's Robotic-arm Assisted Surgery. Accreditation includes attending a Surgical Skills training course provided by Stryker and led by a surgeon experienced with using Mako, review of the planning and surgical technique guides, surgical observation and consultation with current Mako users.

All potential study patients will be assigned a MAKORCT-15 study ID.
If a patient has previously had a MAKO CT Arthrogram and wishes to participate in the study, the patient is required to sign the study approved consent form and the previous MAKO CT Arthrogram will be used for study purposes.
If the patient has previously had a MRI or MRI/CT Arthrogram (within 6 months of planned study surgery date), the patient is required to sign the study approved consent form and the previous MRI or MRI/CT Arthrogram will be used for study purposes. Once the study consent form is signed, the patient will be referred for a MAKO CT for surgical planning purposes.
If a patient has not had a MAKO CT Arthrogram, MRI or MRI/CT Arthrogram and wishes to participate in the study, the patient is required to sign the study approved consent form, and once signed the patient will be referred for a MAKO CT Arthrogram.

If the patient meets the Inclusion and Exclusion criteria and has signed the study consent form, the patient will be enrolled onto the study. If the patient does not meet the Inclusion and Exclusion criteria and has signed the study consent form, the patient will be terminated from the study as a Screen Failure.
Enrolled patients will be randomised to one of two equally sized groups either; the Restoris® MCK Multicompartmental Knee System group or the Triathlon Primary Total Knee System group. Randomisation will take place via the Investigator or designee using the central randomisation system within Inform for allocation to either group. Block randomisation will be performed by a statistician using specialised randomisation software with a block size of 4.

Any deviation from the assigned treatment will be reported as a deviation from Protocol.

8.0 DEVICE DESCRIPTION

All implant components to be used in this trial have been approved for sale and use throughout Australia.
In addition, Stryker's Robotic Arm, comprising of surgical arm guidance module and cameras will be used for intraoperative assessment of implant and limb position. This system is commercially available, and has been approved for sale and use throughout Australia.

8.1 Device Trade Name

<u>The Restoris® MCK Multicompartmental Knee System</u>

The **Restoris® MCK Multicompartmental Knee System** is a commercially available, ARTG listed device. The Restoris® MCK Multicompartmental Knee System is manufactured by MAKO Surgical Corp. 2555 Davie Road, Fort Lauderdale, FL, 33317 USA.

The prosthetic components under study in this protocol include:

- RESTORIS® MCK Multicompartmental Knee System
    - RESTORIS® MCK Femoral Condyle

- RESTORIS® MCK Patellofemoral
- RESTORIS® MCK Tibial base plate
- RESTORIS® MCK Tibial insert onlay
- RESTORIS® MCK Patella Dome (cemented)

Figure 1: The RESTORIS® MCK system, Family of implants

The components of the RESTORIS® MCK system are used to individually treat the components of the knee when showing osteoarthritis. The medial unicondylar and patellofemoral components may be combined to perform a bicompartmental knee arthroplasty. These surgical options are shown below in Figure 2.

Figure 2: Stryker robotic-arm assisted surgery solutions.

Figure 3: The Mako System consists of the RIO® Surgical Arm, RIO® Guidance Module, and the Camera as pictured. The system utilizes tactile robotic arm technology with integrated intelligent surgical instruments and navigation visualization system to pre-plan and treat each patient uniquely. After the implant plan is confirmed the system prevents resection outside of the defined spatial boundaries through an established relationship between the cutting burr and the patient's anatomy. The end effector of the robotic arm is controlled by the surgeon as shown while the system provides the surgeon with real-time visual, tactile and auditory feedback.[7]

Figure 4: Surgeon holding Stryker's Robotic Arm

The comparator (Stryker Triathlon Primary Total Knee System) group:

The **Stryker Triathlon Primary Total Knee System** is a commercially available, ARTG listed device. The Triathlon Primary Total Knee System is manufactured by Stryker Orthopaedics (Mahwah, New Jersey).

The prosthetic components to be implanted as part of this study will collectively be referred to as the **Stryker Triathlon Primary Total Knee System**. Within this system, various

individual implants of different designs, sizes and thicknesses are included. The required components to be used in this study group include:

- CR Femoral Cementless Component – Beaded with Peri-Apatite
- CR Femoral Cemented Component
- Primary Tibial Baseplate – Cemented
- CR Tibial Insert – X3
- CS Tibial Insert – X3
- Triathlon X3 Patella (cemented asymmetric/symmetric)

Figure 3: The Triathlon® Knee system, Family of implants

In addition, the **Stryker Precision Knee Navigation System**, comprising of computer hardware and software and associated instrumentation, will be used for intra-operative assessment of implant and limb position. This system is a commercially available, TGA (Therapeutic Goods Administration) listed device, and has been approved for sale and use throughout Australia.

8.2 Device Supply

All device components will be supplied by the local supplier in Australia in accordance with usual commercial supply.

The Restoris® MCK Multicompartmental Knee System, Triathlon Primary Total Knee System, and Precision Navigation System are supplied by Stryker Australia Pty Ltd.

9.0 SURGICAL PROCEDURES

The Restoris® MCK Multicompartmental Knee System will be implanted using the corresponding instrumentation systems supplied by the manufacturer, as approved for use with this system, and as described in the surgical technique provided by the manufacturer (Appendix 1).

The Triathlon Primary Total Knee System will be implanted using the corresponding instrumentation system supplied by the manufacturer, as approved for use with this system, and as described in the surgical technique provided by the manufacturer (Appendix 2).

Appropriate post-operative care will be given and is at the discretion of the physician.

10.0 INFORMED CONSENT

The Investigator will inform the patient of the purpose of the study, proposed duration of the study, follow-up schedule, method of application and randomisation of study groups. The Investigator will discuss foreseeable risks involved, as well as potential benefits that result from the use of the device. The Investigator will also inform all patients that, should an unanticipated adverse device-related effect occur during the study which, in their opinion presents unreasonable risks to the patients, all patients will be notified and patient enrolment will be terminated. Patient information will be used during the analysis of the results of the clinical study but the confidentiality of the patient will be maintained at all times.

The patients will be informed by the Investigator that they are free to refuse participation in this Investigation; and if they should participate, that they may withdraw from the study at any time without compromising further medical care.

A signed and dated Informed Consent must be obtained by the Investigator or his/her designee from the patient prior to enrolment into this study. The original signed and

dated information sheet and patient consent will be kept by the Investigator. A copy will be provided to the patient.

11.0 EVALUATIONS

All data will be recorded on Case Report Forms or via Electronic Data Capture (EDC). The surgeon or study coordinator will complete and sign forms at the time of each protocol required visit.

The following data will be collected for all patients:

- **Patient Demographics:** A record of the patient's date of birth, gender, height, and weight will be obtained pre-operatively.
- **Medical History:** Relevant medical history will be recorded pre-operatively.
- **Surgical Details:** A summary of the surgical procedure will be collected during the operation. This will include details of the prosthetic components implanted, operating time and comments.
- **Patient outcome measurements:** Surgeon assessment of patient clinical outcomes will be recorded at various study visits. The following outcome scores will be recorded at time points as set out in the patient evaluation schedule. These include pre-operative, 6 week, 3 month, 12 month and 24 month follow-up visits (see Appendix 3)**:**
    - **Oxford Knee Score (OKS):** A 12 item questionnaire was developed to measure outcomes of patients undergoing total knee replacement (Dawson et al. 1998). The score is a self-completed questionnaire that asks patients to answer questions on their pain levels and function (Whitehouse et al. 2005).
    - **EQ-5D *Euro-Qol (EQ-5D-5L)***: The EQ-5D-5L is a standardised patient-completed instrument for use as a measure of health outcome (Fransen and Edmonds, 1999). It consists of 5 dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. There are 5 levels of severity to select from within each dimension.

- ***VAS* Pain:** A graphic Visual Analogue Scale (VAS) used as measurement instrument for patients to indicate their level of pain. The amount of pain that a patient feels is believed to range across a continuum from none to an extreme amount of pain i.e. from the patient's perspective this spectrum appears continuous - their pain does not take discrete jumps, as a categorization of none, mild, moderate and severe (Wewers et al. 1990).

- **Forgotten Joint Score (FJS):** The Forgotten Joint Score is a newly-developed twelve-item, self-reported assessment of how aware recipients of hip and knee joint replacement are of their joint in everyday life (Behrend et al, 2011). These scores have been further validated to demonstrate reproducibility when repeated (Roe et al, 2014). A computer-adaptive test version called FJS-CAT has been developed from the original version which consists of a reduced test length, and had a strong level of acceptance by patients when administered (Giesinger et al. 2013)

- **New Knee Society Score (KSS):** A validated score assessing surgeon generated objective measures based on technical outcomes such as ROM, alignment and stability, and subjective measures based on patient satisfaction, patient expectations and functional activity of the knee (Noble et al. 2012), (Scuderi et al. 2012).

- **Radiographs:** A MAKO CT Arthrogram or MAKO CT will be used for surgical planning and study purposes. Anteroposterior (A/P), and Lateral Knee radiographs will be obtained pre-operatively and ≤5 days postoperatively for immediate assessment. Anteroposterior (A/P), and Lateral knee post-operative radiographs will also be collected 3 months, 12 months and 24 months, as outlined in the Patient Evaluation Schedule. Skyline knee x-rays will be obtained pre-operatively and at 12 months and 24 months post-operatively. The pre-operative radiographs will be compared to radiographs taken post-operatively for assessment of implant positioning and

cartilage wear. All radiographs will be independently reviewed and assessed to quantify any radiographic changes within the region of the study device.

Outlined below are the specifications required for the radiographic images as per the Patient Evaluation Schedule.

A/P Knee: To be performed as a weight bearing A/P x-ray using a 24x30 or 35x43 cassette plate at a 100cm FFD. When using a CR system, please ensure magnification is defaulted to 100%. Coverage to include 3cm above the patella and 3cm below the tibial tuberosity. X-rays collected post op ≤5 days post-surgery will not be performed as weight bearing.

Lateral Knee: To be performed as a weight bearing lateral x-ray using a 24x30 or 35x43 cassette plate at a 100cm FFD. When using a CR system, please ensure magnification is defaulted to 100%. Coverage to include 3cm above the patella and 3cm below the tibial tuberosity. X-rays collected post op ≤5 days post-surgery will not be performed as weight bearing.

Skyline Knee: To be performed in the supine position with the knee flexed at 45 degrees using a 24x30 cassette plate at a 100cm FFD. When using a CR system, please ensure magnification is defaulted to 100%. Coverage to include whole patella and trochlear groove.

- **Adverse Events:** All information on general medical, operative and device related complications will documented and tabulated (see section 19.0 for Adverse Event description and handling).

12.0 STATISTICAL METHODS

12.1 Enrolment and Randomisation

At least **35** patients per study group will be enrolled. Enrolment is defined as meeting the study Inclusion and Exclusion criteria.

The randomisation procedure by which the Knee System for the individual operation will be chosen (**Restoris® MCK Multicompartmental Knee System** versus the **Triathlon Primary Total Knee System**) will be centrally organised for all investigators, and allocated via block randomisation. At the time the patient meets the Inclusion and Exclusion criteria to take part in the study, the surgeon or designee will use the central randomisation system (via Inform) to obtain a randomised allocation. The block randomisation scheme will be performed using randomisation software with a block size of **4**. The randomisation scheme will ensure that during the enrolment period the ratio of the number of cases in the two groups remains approximately constant and that surgical kits are available for each case.

12.2 Sample Size Justification

The change in the Oxford Knee Score (OKS) from pre-op to post-op assessments has a standard deviation of approximately 8.0 (Scott et al, SD=9.8; Walker et al, Table 2, SD=6 for UKR, and SD=8 for TKR). The parameters of the sample size calculation were set as follows: level of significance 0.05, 2-sided test, and postulated difference and standard deviation of 6.0 and 8.0 respectively. For these settings a sample of 29 patients in each arm is required to achieve a power of 80%. The sample size was increased by 20% to 35 in each arm, so 70 in total, in order to allow for withdrawals.

12.3 Data Capture and Analysis

At the commencement of the study, data may be recorded on 2-part NCR paper Case Report Forms (CRFs). Electronic Data Capture (EDC) will be implemented for this study, at which time the sponsor will enter all paper data collected to date and all new patient data will be captured via EDC. Investigators and study coordinators will be trained on EDC completion.

The surgeon or designated signatory will complete and sign forms at the time of completion.

Original paper CRFs will be collected by Stryker for data entry. Copies will remain at the Investigator site. Archiving will be undertaken in accordance with ICH/GCP guidelines (Appendix 5).

Any unclear or ambiguous data will be queried, either via paper queries or electronic queries as applicable and all cleaned data will be analysed.

12.4 Statistical Analysis

For each treatment group the demographic data will be summarised as number of observations, mean, standard deviation, minimum, median, maximum for continuous variables such as age, and as frequency and percentage for categorical variables such as gender.

For the test of the treatment effect the null hypothesis is no difference between the means of the 2 treatment groups, and will be tested against the alternative hypothesis that there is a difference between the means of the treatment groups.

The primary and continuous secondary efficacy variables will be analysed with a mixed model for repeated measurements (MMRM). The model will include factors for treatment group, time, and the interaction between treatment group, and time. For each variable the baseline values will be included in the model as covariate. The treatment effect will be tested against between patient variance. The time effect, and the interaction between treatment group and time will be tested against within patient variance. The results will be summarised as mean, and 95% CI by treatment group, and time. The least squares means will be reported for the treatment difference at each time, and overall with 95% CI. The results will be presented in tabular format, and graphically by treatment group, and time. The continuous variables of change from baseline, and percentage change from baseline will be reported as mean, and 95% CI for each treatment group.

Adverse events will be tabulated separately and reviewed for any commonalities.
The data will be summarised and comparisons presented according to:

- Treatment group : Restoris® MCK Multicompartmental Knee System or Triathlon Primary Total Knee System
- Adverse events: General complications, local complications, device-related complications, revisions/removals, loosening and pain.

In the event of errors in randomisation, the patient will be classified according to the treatment received. All randomisation inconsistencies will be listed.

12.5 Analysis Populations

Intent to Treat Populations

An intent-to-treat analysis will be performed using all patients who were randomised and received a study device. Patients missing the measure of the primary end point (i.e. completed surgery and did not attend the 24 month visit) will be considered missing in the intent to treat analysis; no imputation of missing data will be conducted for any variables.

13.0 SELECTION CRITERIA FOR INVESTIGATORS AND CLINICAL MONITORS

- The Investigator/s selected to participate in this study is/are qualified Orthopaedic surgeon/s.
- Research assistants and study staff will be representatives of the Institute under the direction of the Principal Investigator.
- Any conflicts of interest (including financial assistance from other parties) will be declared by Investigators and research personnel before the commencement of the trial.
- Investigators must maintain a list of any delegated duties with respect to the trial, and the persons and qualifications of those persons to whom the duties are assigned.
- Sites must be able to demonstrate that adequate subject recruitment is likely to be possible, with necessary time available to conduct the study to GCP requirements, and with adequate facilities and trial staff.

- Investigators must provide medical care to a trial participant that is necessary as a result of any adverse event experienced during or following the trial that is deemed related to the trial.
- Investigators must possess, prior to trial commencement, a favorable Ethics Committee endorsement of trial protocol, Patient Information and Consent forms and any other information given to subjects.
- All trial related documents are subject to Ethics Committee review. A regular trial report is also mandatory for provision to the Ethics Committee (in accordance with local requirements).
- The Investigator/Institution shall permit trial related monitoring, audits, Ethics review and regulatory inspections, by providing direct access to source data/documents and any other trial related documentation.
- The trial MUST be conducted according to the approved protocol.
- Any deviation from the protocol must be documented for later review.
- No deviation from protocol may occur without Ethics Committee endorsement, unless it is required to prevent imminent harm to participants
- Investigators must ensure subjects have given informed, written consent, with all trial procedures and risks adequately explained.

14.0 ADMITTANCE OF PATIENT

The Investigator must wait for written Ethics Committee and Governance approval prior to beginning the study or enrolling participants.

A patient will be identified as a patient in this clinical trial upon signing a Patient Information Sheet and Consent form.

A review of the inclusion and exclusion criteria must be completed by the Investigator pre-operatively for each patient.

15.0 PATIENT ACCOUNTING

The Investigator or designee will complete an informed consent log with details (patient number and initials) of any patient signing a consent form to participate in this study.

Clinical trial data will be monitored regularly to identify any trends and adverse events. Documentation of participants who voluntarily withdraw from the study or who are lost to follow-up will be obtained on a Study Termination Form.

16.0 QUALITY ASSURANCE OF DATA

Case Report Forms (CRFs) or electronic Case Report Forms (eCRFs) will be routinely reviewed by the Principal Investigator for completeness and accuracy as well as any evidence which may be indicative of patient risk. When any discrepancies are noted, they will be resolved with the Investigator and/or individual designated by the Investigator. When the data are incomplete, attempts will be made to obtain the data whenever possible.

Clinical Research staff from Stryker Australia will monitor the investigational site at regular intervals to ensure compliance with the protocol and capture of any data or complications not already documented. Verification of the data from source documents will also be conducted by the Stryker monitors.

17.0 MANAGEMENT OF INTERCURRENT EVENTS

17.1 Concurrent illness/procedures

Participants requiring concurrent procedures or medications for inter-current illnesses or adverse events will not be restricted throughout the study. Given the typical patient population receiving knee joint replacements, it can reasonably be expected that concurrent illnesses or procedures may be experienced by study participants.

17.2 Withdrawal from Study

Participants will be advised that they may voluntarily withdraw from the study at anytime, for any reason and they are not obligated to reveal the reason to the Investigator and it will not affect their medical care. However, in such cases, appropriate effort will be made to determine the reason for withdrawal from the study. The Investigator may request a letter from the patient noting his or her desire to withdraw from the study. All attempts to locate participants lost to follow up will also be documented.

Participants will be informed that should they withdraw from the study they should remain under the care of an appropriately experienced physician until the physician deems further follow-up unnecessary.

The following are circumstances for which a patient would be identified as not continuing their participation in the study:

- Study Completed / Terminated
- Screen Failure
- Death
- Unable to Return
- Unwilling to Return
- Concurrent Illness
- Lost to follow-up
- Re-operation of the affected knee joint, including revision of knee replacement components
- Incorrect implant(s)/device(s) used, device not included in protocol
- Other

Additionally, the patient may be withdrawn by the Investigator, if he/she is unable to continue participation in the study due to some condition unrelated to this study.

A Study Termination Form will be completed for all participants who withdraw from the study.

18.0 MODIFICATION OF PROTOCOL

No changes to this protocol will be permitted without the written approval of the applicable Ethics Committee.

Protocol deviation details, including the type of deviation (e.g. informed consent, inclusion/exclusion criteria, treatment, tests or visits not performed) should be recorded on a Protocol Deviation Form as soon as identified and notification will be made to the applicable Ethics Committee according to the Ethics Committee requirements.

19.0 DEFINITIONS AND REPORTING OF ADVERSE EVENTS

19.1 Definitions

Adverse Events:

Any undesirable clinical occurrence in a subject, whether it is considered to be device related or not, that includes a clinical sign, symptom or condition and/or an observation of an unintended technical performance or performance outcome of the device.

Expected: An adverse event is expected when the specificity and severity of the event is consistent with a complication that is not related to the device but may be related to the surgical procedure.

Unexpected: An adverse event is unexpected when the specificity or severity of an adverse event is not consistent with the standard. It refers to an adverse event that has not been observed before.

Adverse Device Event

A clinical sign, symptom or condition that is causally related to the product, implantation procedure, the presence of product or the performance of the device system.

Serious Adverse Advent (SAE):

Any untoward medical occurrence that:

- Results in death,
- Is life threatening,
- Requires inpatient hospitalization or prolongation of hospitalization*,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or;
- Is a medical or surgical intervention to prevent life-threatening illness and injury or permanent impairment to a body structure or a body function.

*Planned (elective) hospitalization for a preexisting condition (a condition that is captured on the pre-op clinical data/medical history CRF), or a procedure required by the protocol, without serious deterioration in health, is not considered a Serious Adverse Event for this study.

Examples of such elective procedures include, but are not limited to, the following commonly seen events:

- Contralateral Total Knee Replacement or Partial Knee Replacement
- Total Hip Replacement
- Cataract Surgery

Such events should not be categorized as SAEs on the Stryker AE/SAE Reporting Form, but rather should be classified as Adverse Events.

Cancer should be captured as one SAE per diagnosis. All related follow up treatments for the primary cancer diagnosis, including in-patient Chemotherapy or Radiotherapy should be captured as new information for the same SAE (the SAE can be left as unresolved with status date changed each times updates are made to the treatment section.) All metastasized (secondary) cancer diagnoses and associated treatments should be captured on a new SAE form.

19.2 Reporting of Events

Any serious adverse event that occurs between patient consent and end of study, or adverse event that occurs from surgery to end of study will be recorded as such.

Additionally, any adverse event identified during radiographic review, will be recorded as such.

Adverse Events:

Any adverse event should be recorded as follows:

All information on general medical, operative and device related complications (adverse events) will be documented on Case Report Forms (CRFs) or electronic Case Report Forms (eCRFs). Information should include date of occurrence, description, severity, relationship to study device, treatment and date of resolution.

The Investigator must determine if the event is related to the device. Any adverse event in a study patient must be monitored until the event is resolved or considered non-clinically significant by the Investigator.

Expected Events: Should be reported to the Sponsor soon as possible, but not later than ten working days after the Investigator first learns of the effect.

Adverse Device Events

Should any adverse device events occur, the study staff will ensure that these are documented by the Investigator and reported immediately to the Sponsor. They should also be reported to the reviewing Ethics Committee and Institution as soon as possible, but not later than fifteen working days after the Investigator first learns of the effect, unless an earlier timeline is specified by individual study sites. The Investigator with the Sponsor will conduct an evaluation of such effects. Following this evaluation, if the Investigator determines that an unanticipated adverse device effect presents an unreasonable risk to participants, the Investigation will be terminated as soon as possible. Termination shall occur no later than five working days after the Investigator makes this determination and

no later than fifteen working days after the Investigator first receives notice of the unanticipated adverse effect.

Serious Adverse Events:

Any adverse event that is considered to be of serious nature and occurs at any time point from the signing of Informed Consent Form until either the patient is terminated from the study, or 30 days post-completion, should be recorded as follows:

All Serious Adverse Events (SAEs) should be reported immediately to the Sponsor by email or fax, **no later than 24 hours** after becoming aware of the event. The immediate reports should be followed promptly by detailed, written reports. Reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names and/or addresses. The Investigator should also comply with the applicable regulatory requirement(s) related to the reporting of serious unexpected adverse device reactions to the regulatory authority (TGA) and the Ethics Committee. All other SAEs that are NOT related to the device will be reported to the Ethics Committee in a table with the annual reports, or as otherwise directed by the relevant Ethics Committee.

20.0 ETHICS COMMITTEE

20.1 Approval

The Investigator is responsible for obtaining Ethics Committee approval to conduct this study.

20.2 Prior to Initiation of the Study

The Investigator must wait for written approval by the Ethics Committee and Governance Officer prior to beginning the study. The Investigator may discuss the study with prospective participants; however, the Investigator may not obtain written Patient Informed Consent, nor perform study procedures on prospective study participants, until all required approvals are granted.

20.3 Progress Reports

The Investigator will also submit, at intervals requested by the Ethics Committee, progress reports on this study. These progress reports will be submitted both to the Sponsor and to the Investigator's Ethics Committee.

20.4 Withdrawal of Ethics Committee Approval

Should the Ethics Committee withdraw its approval, the Investigator will notify the Sponsor no later than five working days following such withdrawal.

20.5 Final Reports

Upon completion of the study, the Investigator will submit a Final Report on the Investigation within three months of completion of the Investigation. This report will be submitted both to the Sponsor and the Investigator's Ethics Committee.

21.0 SPONSOR RESPONSIBILITIES

21.1 Reports

The Sponsor, upon completion of the study, will prepare a comprehensive Final Report. These reports will be submitted to the Investigator/s, and ethics committee/s.

21.2 Clinical Monitoring of the Study

The Sponsor will monitor and ensure that this study is conducted in accordance with the signed Investigator Clinical Investigation Research Agreement, the Protocol, conditions imposed by the Ethics Committee, as well as other applicable regulations. Prior to initiating any study related activities, the Sponsor will conduct an appropriate pre-investigational visit and further communication to ascertain that:

- The Investigator/s understand and accept his/her obligation in conducting the study
- The Investigator/s understand the use of the device
- The Investigator/s and staff have sufficient time and access to the adequate number of subjects required for the study

- The Investigator/s understand that the study does not begin until written approval of the protocol is obtained from the ethics committee and all conditions of the ethics committee approval have been met
- The Investigator/s and study staff understand and can complete the required case report forms
- The Investigator/s have signed a Clinical Investigation Research Agreement and have a current curriculum vitae on file
- The Investigators ethics approval is on file.

During the course of the study, the clinical monitors conduct periodic visits at intervals and maintain regular contact with the Investigator/s and his/her staff to ascertain completeness and accuracy of data being collected as well as any evidence which may be indicative of subject risk. When any discrepancies are noted in the data, they will be resolved with the Investigator/s or his/her designee. When data are incomplete, they will be obtained whenever possible.

The Monitor will report to the Stryker Clinical Research Manager any non-compliance by the Investigator with the signed Clinical Investigation Research Agreement, the Protocol, the requirements of any TGA regulation, or any condition imposed by the reviewing ethics committee. The Sponsor will secure compliance from the Investigator or terminate the Investigator's participation in the study. Ethics Committee approval will be obtained prior to resuming a terminated Study. Should any deviations from the Protocol occur, these will be reviewed by the monitor for their clinical significance and appropriately documented and reported.

22.0 USE OF INFORMATION AND PUBLICATIONS

Investigators must respect the confidentiality of data, especially regarding its use by potential competitors and must abide by conditions as agreed to in the Clinical Investigation Research Agreement.

The information gathered during this study will be disseminated in journals and conferences. Anonymity of the participants involved in the study will be maintained at all times.

23.0 ANALYSIS/CONCLUSIONS

The data obtained in this Investigation will be maintained and periodically assessed throughout the study.

A formal interim analysis will take place following all patients' completion of the 12 month post-operative visit. The interim analysis will aim to review functional outcomes out to 12 months post-surgery.

The final analysis will take place following all 24 month follow-up visits.
Based on the above design and planned analysis, we believe this protocol is scientifically sound and that the clinical evaluation of the experimental procedure is justified.

24.0 BIBLIOGRAPHY

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APPENDIX 1

Restoris® MCK Planning and Surgical Technique Guide

APPENDIX 2

Triathlon Knee System – Express Instruments Surgical Protocol

APPENDIX 3

QUESTIONNAIRES

a) Oxford Knee Score
b) EQ-5D Questionnaire
c) VAS pain
d) Forgotten Joint Score
e) Knee Society Score

APPENDIX 4

DECLARATION OF HELSINKI

APPENDIX 5
TGA ANNOTATED ICH GCP