PROTOCOL: ShapeNZRCT-10 (with ShapeNZEx-13 Extension Study)

Version: 4.0

Date: 25 March 2014

A prospective, randomized, controlled trial of Mechanical Axis vs. Kinematic Alignment in Total Knee Replacement – A study using Stryker PrecisioN Knee Navigation and Stryker Triathlon® Custom Fit Knee® Featuring OtisMed® ShapeMatch® Technology.

With Extension Study:

A follow-up, longitudinal study of the clinical and radiographic outcomes of participants who received a Stryker Triathlon® Custom Fit Knee® using either Stryker PrecisioN Knee Navigation or OtisMed® ShapeMatch® Technology

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I have read and agree to follow this protocol and the New Zealand Health Research Council (HRC) Guidelines on Ethics in Health Research:

Principal Investigators:

Mr William Farrington	_____ Signature	__/__/__ Date
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1.0 SUMMARY

This is a prospective, randomized, longitudinal study of the clinical outcomes of osteoarthritis patients treated by two different alignment philosophies for total knee replacement. Participants will be treated using the Stryker Triathlon® Total Knee System for Total Knee Arthroplasty (TKA) implanted using either Stryker OtisMed® ShapeMatch® Technology (intervention) or Stryker PrecisioN v4.0 Knee Navigation (control). Health status and functional outcome measures will be recorded to quantify functional status of subjects before surgery and at each follow-up interval. An economics analysis will also be conducted to compare costs associated with each technology platform.

There will be 2 sites (North Shore Hospital, Auckland and Waitakere Hospital, Waitakere), 1 Principal Investigator and 6 co-Investigators for this study. A maximum of 50 cases will be enrolled in each group, for a total of 100 patients. It is expected that participants will be recruited over a 6 month period. Total duration of the study is expected to be 1.5 years.

The study consists of two groups:

1. Intervention Group: Treatment by total knee replacement with a target lower limb alignment determined using pre-operative imaging and kinematic alignment, implemented using Stryker OtisMed® ShapeMatch® Technology;

2. Control Group: Treatment by total knee replacement with a target lower limb alignment equal to neutral Mechanical Axis, implemented using Stryker Knee Navigation.

Pre-operatively, all participants will be required to undergo medical imaging assessment using Magnetic Resonance Imaging (MRI) of the affected lower limb. These images will then be used to manufacture the patient-specific cutting guides for preparation of the bones prior to implantation of the total knee replacement.

All participants (control and intervention groups) will be requested to attend visits pre-operatively and post-operatively at 6 weeks, 6 months and 12 months. At these visits participants will complete assessments relating to quality of life, pain and functional

outcome. In addition, participants will have standard knee X-rays taken pre-operatively and post-operatively. A post-operative CT scan will be obtained for all participants in order to assess implant position and orientation.

All devices used in this study have been registered with MedSafe NZ and are approved for sale and use in New Zealand.

This study will adhere to all relevant requirement and guidelines in relation to the conduct of clinical trials, including the Declaration of Helsinki (Appendix 5) and ICH Good Clinical Practice Guidelines, as implemented in New Zealand (Appendix 6).

An Extension Study will be undertaken to follow all patients (intervention and control group) who consent to continued follow-up. These patients will be followed out to 5 years post-surgery, with a follow up visit at 2 years and 5 years, to collect longer term data on radiographic and patient outcomes. Data will also be captured on the secondary objectives of revision rate, device-related adverse events and re-operation rates.

Visit Windows

Definition – Since it is not always possible for subjects to come in for a study visit on the exact date, most protocols allow a certain time period before or after the calendar date; this is known as the visit window. If a subject is not seen during the visit window, that visit will be regarded as a missed visit. Visit windows are calculated in reference to the baseline date, which is the surgery date (intra-op) for this study.

Patient Evaluation Schedule for All Patients

EVALUATION	History/ Pre-Op	Intra-Op	6 week	3 MO*	6MO	12MO
Demographics	✓					
Medical History	✓					
MRI	✓					
Surgical Details		✓				
Oxford Knee Score	✓		✓		✓	✓
IKSS	✓		✓		✓	✓
FJS-12			✓		✓	✓
WOMAC	✓		✓		✓	✓
EQ-5D-3L	✓		✓		✓	✓
VAS Pain	✓		✓		✓	✓
AP and ML X-rays	✓		✓			✓
Perth CT Protocol				✓		

*3 month patient visit is non-standard, i.e. in addition to the usual follow-up routine for TKA patients.

The visit windows for this study are:

- Pre-Op = Within 2 months before the date of surgery
- Intra-op = Baseline time point
- 6 Weeks = +/- 2 weeks
- 3 Months = +/- 6 weeks (no patient visit CT scan only)
- 6 Months = +/- 1 month
- 12 Months = +/- 2 months

Extension Phase

EVALUATION	2 year follow-up	5 year follow-up
Demographics	✓	
Medical History and Surgical Details Review	✓	
Oxford Knee Score	✓	✓
IKSS	✓	✓
FJS-12	✓	✓
WOMAC	✓	✓
EQ-5D-3L	✓	✓
VAS Pain	✓	✓
AP and ML X-rays	✓	✓
Long-leg weight-bearing x-rays	✓	✓

The visit windows for this study are:

- 2 years = +/- 6 months
- 5 years = +/- 6 months

2.0 INTRODUCTION

Total Knee Replacement (TKR) has evolved to a point where implant design combined with instrumentation and surgeon skill results in excellent implant survival. The New Zealand National Joint Register reported over 6000 knee replacements performed in New Zealand in 2009, with annual figures increasing over the last 10 years.

Total Knee Replacements are undertaken to treat a range of conditions including osteoarthritis, rheumatoid arthritis, avascular necrosis and secondary arthritis resulting from trauma.

Current surgical techniques make use of generic, re-usable instrumentation, consisting of intra- and/or extra-medullary rods on the femur and tibia to determine alignment in relation to anatomical landmarks, combined with bone resection guides

which ultimately determine position and orientation of the definitive implant components.

Traditionally, the goal of TKR has been to position the components such that the post-operative alignment goal is a straight limb, or a mechanical axis of 0° (Insall & Scott, 2001). The mechanical axis is defined by lines joining the centre of the femoral head, centre of the knee joint and the centre of the ankle. Despite the best efforts of the surgeon, the resulting limb alignment varies away from 0° by a small amount (typically less than ±3° in 80% of cases).

More recently, the use of computer navigation systems has been introduced to surgical practice with the aim of improving the ability to obtain post-operative limb alignment as close as possible to 0° (Chauhan et al, 2004).

Whilst achievement of neutral limb alignment has been considered desirable from an engineering point-of-view – to maximize implant longevity through minimizing the deleterious effects of polyethylene insert wear and particle-induced osteolysis and implant loosening – patient satisfaction of TKR has not always been ideal. Despite surgery being performed technically correct by surgeons, up to 1 in 5 patients express dissatisfaction in the functional result (Bourne et al, 2009). Patient expectations after surgery are also increasing due in part to the adoption of more active lifestyles amongst total knee replacement recipients where return to function can be of primary importance.

The opportunity exists to provide an alternative approach to TKR surgery which may result in improved patient outcomes. One such approach is to determine the optimal placement of components based on the individual anatomy of patients, rather than a generic limb alignment philosophy (Coughlin et al, 2003; Eckhoff et al, 2005). This approach relies on the creation of a pre-arthritic model of the bone and cartilage structures of the knee. A single, 3-D axis of rotation is then determined which takes into account the 3-D shape and orientation of the femoral condyles during the weight-bearing portion of gait. This is in contrast to traditional surgical techniques which set femoral component orientation and position using one or more of the trans-epicondylar axis, posterior-condylar axis and/or the anterior-posterior (or Whiteside's)

line. This new axis is then the basis of determining the so-called natural alignment goal for the joint replacement procedure.

A comprehensive three-dimensional description of the anatomy can be obtained by magnetic resonance imaging (MRI) scans obtained pre-operatively. Through a proprietary process, it is possible to pre-operatively develop a model of the arthritic bone and cartilage, adapt that model to take into account degenerative process, and generate a model of the pre-arthritic anatomy (Fig. 1). The pre-arthritic state then becomes the surgical goal in terms of limb alignment. Custom cutting guides are generated for each individual patient to enable the surgeon to perform the bone resections in such a way that the resultant construct with the TKR components reproduces the pre-disease limb alignment (Fig. 2). Early experience of applying this technique indicates that patient outcomes and function assessed during the early post—operative phase are superior to conventional approaches to TKR (Howell et al, 2008; Spencer et al, 2009). Other potential advantages of this technology include a reduction in blood loss (as no intramedullary rod is used), and a reduction in ligament releases (as the total knee components effectively resurface the knee with restoration of the natural alignment) (Howell et al, 2008).

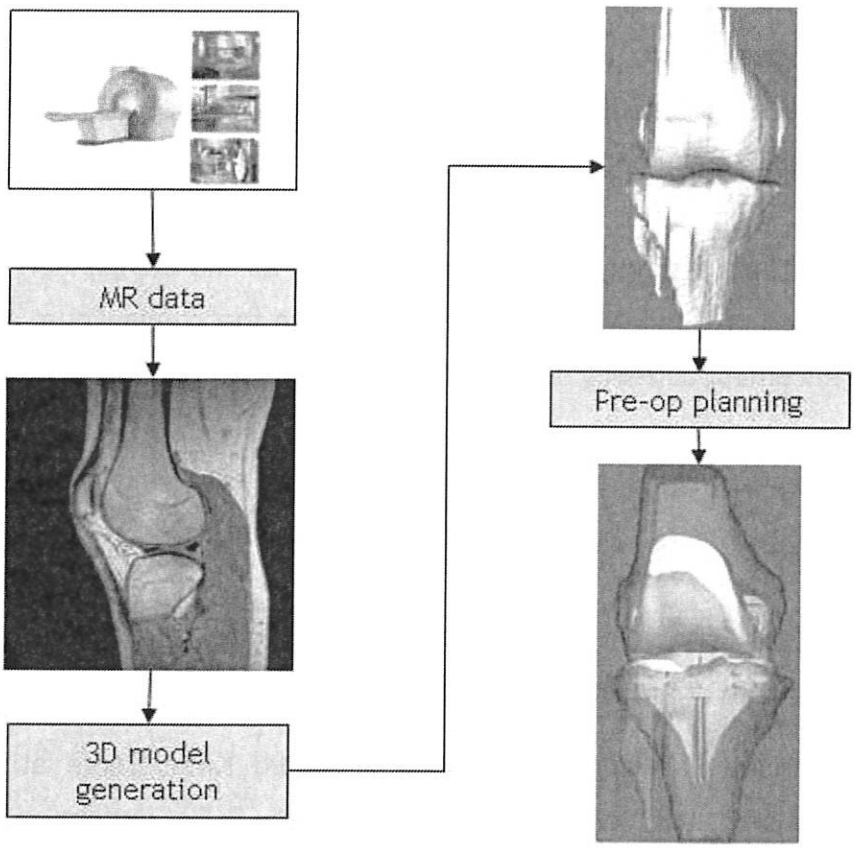

Figure 1: Workflow and data transfer process used for preparation of ShapeMatch® cutting guides.

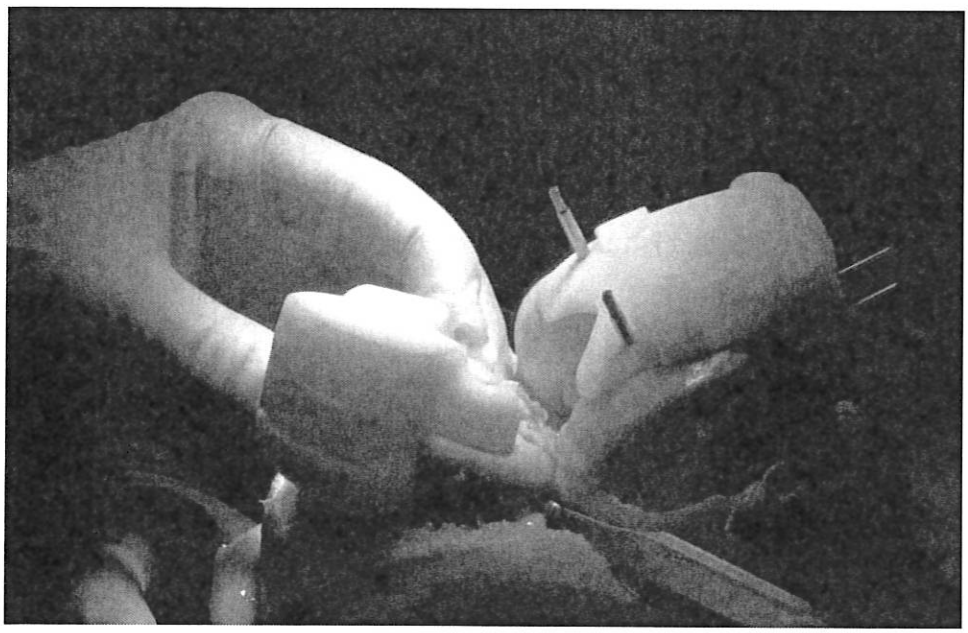

Figure 2: Intra-operative image of ShapeMatch® cutting guides positioned on distal femur and proximal tibia. Femoral cutting guide has been pinned in place, ready for bone resection. Tibial cutting guide being positioned prior to pinning.

A consecutive cohort study is underway in Australia to test this reproducibility in osteoarthritic patients and to further follow the patient outcome to 6 months following surgery with ShapeMatch® cutting guides.

This protocol outlines a randomized controlled study for the comparison of this new approach, the use of ShapeMatch® cutting guides, to the conventional approach to total knee replacement currently used as the standard of care by the Investigators.

Following on from this study, an extension study will be undertaken to determine the clinical and radiographic outcomes out to 5 years post-surgery.

3.0 OBJECTIVES

The primary objective of this study is:

- To demonstrate, through calculation of Oxford Knee Score at 12 months postoperative, that total knee replacement (TKR) performed using the ShapeMatch® Cutting Guide provides improvement from preoperative levels of patient pain and function comparable to the improvement obtained with TKR performed using computer-assisted Navigation. Oxford Knee Scores will be calculated pre-operatively and at 6 weeks, 6 months and 12 months post-operatively.

The secondary objectives of this study are:

- The efficacy objective is to compare radiographic, pain, function and health-related quality of life (QOL) between the ShapeMatch® Cutting Guide group and the computer-assisted Navigation control group. This objective will be achieved by utilizing the following instruments pre-operatively and at the 6-week, 6-month and 12 month visits:
    - Perth CT protocol
    - AP and ML X-rays
    - Oxford Knee Score
    - The International Knee Society Score (IKSS)

- The Forgotten Joint Score (FJS-12)
- WOMAC
- EQ-5D-3L
- VAS Pain

- To compare the cost-effectiveness and cost-utility of the procedure between the ShapeMatch® Cutting Guide group and the computer-assisted Navigation control group. This objective will be assessed by recording and calculating the following parameters:
  - Wound length
  - Total duration of operating procedure (anaesthetic time and skin-to-skin incision time)
  - Cost of consumable items used during operating procedure
  - Length of stay in hospital
  - Quality-adjusted life-years (QALYs) from EQ-5D-3L

The hypothesis is that there is a statistically significant improvement in functional outcome 12 months following a primary Total Knee Replacement when kinematic limb alignment (using ShapeMatch® Cutting Guide) is used compared to that resulting from a goal of neutral mechanical axis alignment (using computer-assisted Navigation).

The Extension Study Primary Objective is:

- To determine the clinical and radiographic outcomes at 2 years and 5 years post-surgery, in patients receiving a Stryker Triathlon® Total Knee System for Total Knee Arthroplasty (TKA) implanted using either Stryker OtisMed® ShapeMatch® Technology (intervention) or Stryker PrecisioN v4.0 Knee Navigation (control).

The Extension Study Secondary Objectives are:

- To determine the revision rate, device-related adverse events and reoperation rates.

4.0 NUMBER OF PARTICIPANTS

A total of 100 participants will be recruited:

- 50 cases will be performed using the Stryker ShapeMatch® Cutting Guides to achieve kinematic alignment (Intervention Group).
- 50 cases will be performed using computer-assisted Navigation and conventional instruments to achieve neutral mechanical axis alignment (Control Group).

Extension study: Patients from both the intervention and the control groups will be invited; a maximum of 100 patients will be included.

5.0 LENGTH OF STUDY AND PATIENT PARTICIPATION

The enrolment period is expected to be 6 months or until the required sample size is reached. Participants in both the Control Group and Intervention Group will be followed for 12 months post-surgery. It is anticipated that the entire study will take approximately 18 months to complete, excluding data analysis.

Following the 12 month follow-up visit, patients will receive an invite to continue participation in the study via enrollment into the Extension Study. Patients will need to meet the inclusion and exclusion criteria for the study (see sections 6.3 and 6.4) and provide informed consent in order to participate.

6.0 PATIENT SELECTION CRITERIA

Each 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. Any patient enrolled in this study who does not meet the inclusion and exclusion criteria will be considered a protocol deviation.

6.1 Inclusion Criteria

- The patient is a male or non-pregnant female between the ages of 40-80 years.
- The patient requires a primary total knee replacement and is indicated for computer-assisted surgery.

- Patient is deemed appropriate for a cruciate retaining knee replacement.
- The patient has a primary diagnosis of osteoarthritis (OA).
- The patient has intact collateral ligaments.
- The patient is able to undergo MRI scanning of the affected limb.
- The patient has signed the study specific, ethics-approved, Informed Consent document.
- The patient is willing and able to comply with the specified pre-operative and post-operative clinical and radiographic evaluations.

6.2 Exclusion Criteria

- The patient has a history of total, unicompartmental reconstruction or fusion of the affected joint.
- Patient has had a previous osteotomy around the knee.
- The patient is morbidly obese (BMI ≥ 40).
- The patient has a deformity which will require the use of stems, wedges or augments in conjunction with the Triathlon Total Knee System.
- The patient has a varus/valgus malalignment ≥ 15° (relative to mechanical axis).
- The patient has a fixed flexion deformity ≥ 15°.
- The patient has a neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device.
- The patient has a systemic or metabolic disorder leading to progressive bone deterioration.
- The patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements.
- Patient has a cognitive impairment, an intellectual disability or a mental illness.
- The patient is pregnant.
- The patient has metal hardware present in the region of the hip, knee or ankle (as this is known to create geometrical distortion in the region of the implant).
- The patient has any known contraindications for undergoing assessment by MRI (e.g. ferrous implants, metallic clips, magnetically activated implanted devices such as cardiac pacemakers, etc.).

6.3 Extension Study: Inclusion Criteria (applicable to patients electing to continue participation in the Extension Study)

- Patient was enrolled in ShapeNZRCT-10 and completed either the 6 month or 12 month follow-up visit (or both).
- Patient is willing and able to give informed consent to participate in the study.
- Patient is willing and able to comply with the specified clinical and radiographic evaluations.

6.4 Extension Study: Exclusion Criteria (applicable to patients electing to continue participation in the Extension Study)

- Patient no longer has the Triathlon® Total Knee System in situ, including patients that have had revision surgery.
- 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.
- Patient no longer resides in a geographical location that would reasonably permit clinic visits at protocol specified intervals.

7.0 STUDY DESIGN

This study will be conducted as a randomised controlled trial, designed to limit confounding bias. Participants will be recruited and assessed against the Inclusion and Exclusion criteria. If participants met these criteria they will be randomised to either the Control Group or the Intervention Group, with no other factors of influence.

This will be achieved via a block randomisation process. A central randomisation list will be computer generated by a consultant statistician. Once a patient has met criteria for enrolment, the Principal Investigator or designee will phone/email the Sponsor with the Initials, Date of Birth and Patient Number (assigned in ascending order at time of recruitment). A randomisation number, corresponding to a randomisation envelope held at the study site, will be provided. Once this number is received the envelope will be located and opened. The Principal Investigator will note the group allocation in the Case Report Form.

Patients will be blinded to their group allocation. This will allow minimal bias when completing post-operative questionnaires.

Pre- and post-operative x-rays will also be reviewed by a blinded reviewer.

Control Group – Neutral Mechanical Alignment using Navigation

Participants randomised to the Control Group will undergo Total Knee Replacement (TKR) with the goal of neutral alignment to the mechanical axis. This is the standard method for TKR with Triathlon® Knee System and this group will serve as a control reference for the intervention group.

Intervention Group – Kinematic Alignment using ShapeMatch®

Participants randomised to the Intervention Group will undergo TKR with the goal of kinematic alignment, re-aligning the limb to its pre-disease kinetic alignment.

Both groups will undergo treatment in parallel. The study will be conducted as a two-centre study with approximately 7 surgeons performing surgery for this study.

Patients will be followed up until 12 months post-surgery and those participating in the extension study will be followed until 5 years post-surgery.

8.0 DEVICE DESCRIPTION

8.1 Device Trade Name

The prosthetic components to be implanted as part of this study in both the Control Group and the Interventional Group include:

- Triathlon® Cruciate Retaining (CR) Total Knee System (cemented), including Femoral Component and Primary Tibial Baseplate;
- Triathlon® Cruciate Substituting (CS) X3® polyethylene insert;
- Triathlon® X3 Patella (asymmetric) – treated selectively by surgeon.

The instruments used to resect the distal femur and proximal tibia as part of this study will differ between the Control Group and Intervention Group. The instruments used

in the Control Group will be the conventional, approved instruments used with the above listed Triathlon® products.

The instruments used in the Interventional Group will be the approved ShapeMatch® Cutting Guide (including Femoral and Tibial cutting guides). These devices are single-use, patient-specific instruments.

The above named products are commercially available, MedSafe NZ listed devices (notified on the NZ WAND Database), and are approved for sale and use throughout New Zealand.

In addition, the Stryker PrecisioN Knee (4.0) Navigation System, comprising of computer hardware and software and associated instrumentation, will be used for intra-operative alignment and orientation of implant in the Control group. This system is also a commercially available, MedSafe listed device, and approved for sale and use throughout New Zealand.

8.2 Device Supply

The ShapeMatch® cutting guides will be supplied by Stryker New Zealand Ltd.
All other devices used in this study are commercially available products which will be obtained via the usual ordering and payment process.

9.0 SURGICAL PROCEDURES

Control Group: Each patient will be prepared to undergo a primary total knee replacement using the Triathlon Primary Total Knee System and Stryker PrecisioN Knee Navigation System. A standard skin incision and joint exposure will be performed according to the surgeon's preference. Navigation trackers will be secured to the femur and tibia and registration of the limb will be undertaken according to the PrecisioN Knee System surgical technique.

Femoral and tibial resections, followed by device implantation, will be performed according to the Triathlon Knee System Surgical Protocol.

Appropriate post-operative care will be provided according to the preference of the treating physician. Post-operative assessments will be undertaken according to the study protocol.

Intervention Group: Each patient will be prepared to undergo a primary total knee replacement using the Triathlon Primary Total Knee System, implemented using Stryker OtisMed® ShapeMatch® Technology. A standard skin incision and joint exposure will be performed according to the surgeon's preference.

The appropriate Stryker ShapeMatch® Cutting Guide will be positioned onto the distal femur, and secured in place using fixation pins. The distal femoral bone resection will be completed and the block removed. Completion of the bone preparation of the distal femur will be undertaken using manual instruments.

The same procedure will be performed on the proximal tibia using the appropriate Stryker ShapeMatch® Cutting Guide.

The surgeon will implant the knee prostheses following the surgical protocol for Triathlon® Knee System with OtisMed® ShapeMatch® Technology (Appendix 1).

Appropriate post-operative care will be provided according to the preference of the treating physician. Post-operative assessments will be undertaken according to the study protocol.

10.0 INFORMED CONSENT

The Investigator will inform potential study candidates of the purpose of the study, proposed duration of the study, including the study-specific procedures and evaluations. The Investigator will discuss foreseeable risks involved, as well as potential benefits that may result for future participants through the outcomes of this study. Following this verbal discussion with the Investigator, participants will then be given time to read, understand, and, if agreeable, sign the study-specific Participant Consent Form indicating their agreement to participate in the study.

De-identified patient information will be used during the analysis of the results of the clinical study and the confidentiality of the participants will be maintained at all times. Patient records will be stored with the surgeon's normal secure record storage system.

The participants will be informed by the Investigator that they are free to refuse participation in this Investigation, and if they decline or withdraw from the study at any time this will not compromise further medical care.

A signed and dated Participant Consent Form must be obtained by the Investigator from the patient prior to enrolment into this study. The original signed and dated Patient Information Sheet and Consent Form will be kept by the Investigator. A copy will be provided to the patient, and another copy placed in the patient's hospital medical record.

Should a patient undergo any study procedure without signing a Participant Information and Consent Form, the Investigator must notify the applicable Ethics Committee and study Sponsor of the deviation, detailing the circumstances which resulted in the failure to obtain informed consent. The Investigator will then follow Ethics Committee instructions on how to handle patient/situation and obtaining consent.

Patients willing to participate in the extension study will undergo a second informed consent process with a new patient information sheet detailing the additional study-specific procedures. This process will be carried out in the same manner as the original informed consent process.

11.0 EVALUATIONS

All data will be recorded on the Case Report Forms. The designated signatory (e.g. Investigator, delegated authority, participant, etc.) will complete and sign forms at the time of each required visit specified by the study protocol.

All participants will have detailed information collected pre- and post-operatively as part of their involvement in this study. Participants will be assessed at 6 weeks, 6 months and 12 months after surgery.

The following data will be captured throughout the study:

Patient Demographics: A record of the patient's date of birth, gender, height, weight, and medical history will be obtained pre-operatively and reviewed again for the Extension Study.

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. Data relating to the number of instruments sterilized and used during each surgical case will be collected. Parameters relating to the effect of each instrumentation platform on costs and efficiency within the hospital environment will also be assessed. These details will be reviewed again for those patients continuing into the Extension study.

Medical Imaging (and Extension Study participants):
Standard Anterior-Posterior (AP) and Medio-Lateral (ML) X-rays of the affected limb will be obtained pre-operatively and post-operatively to assess implant stability.

Extension Study participants will undergo **two Long Leg AP** weight bearing x-rays to evaluate alignment of the limb; one at 2 years and 5 years post-surgery.

An MRI scan according to the OtisMed Imaging Technique will be undertaken pre-operatively to obtain detailed three-dimensional detail of the affected knee and will be transferred to Stryker OtisMed, Alameda CA for development of customized cutting guides. To maintain blinding of participants, both the Control Group and the Interventional Group will undergo MRI scanning.

A CT scan will be obtained 3 months after surgery according to the Perth CT protocol. A published technique will also be undertaken to obtain detailed three-dimensional descriptions of the position and orientation of the implanted components (Appendix 3;

Chauhan et al., 2004). Limb alignment and TKR component position will be compared to the alignment goal for patients in each of the two groups.

Patient outcome measurements (see Appendix 4)**:**

Oxford Knee Score: A patient-completed 12-item questionnaire, designed specifically for patients undergoing total knee replacement. Each of the 12 items has 5 scoring categories. It is short, practical, reliable, valid and sensitive to clinically important changes over time (Dawson et al, 1998).

***The International Knee Society System (IKSS)*:** a universally-accepted tool for assessment of TKR clinical and functional outcomes. It separates findings in the operated knee with findings in the patient's function. As such the Knee Score is not artificially affected by co-morbid conditions. The Knee Score consists of points given for pain, range of motion, and stability in both the coronal and sagittal planes, with deductions for fixed deformity, and extensor lag. The Function Score consists of points given for the ability to walk on level surfaces, and the ability to ascend and descend stairs, with deductions for the use of external supporting devices (Insall et al., 1990).

FJS-12: 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., 2010).

WOMAC: The Western Ontario and McMaster Universities Arthritis Index is a set of standardised self-administered questionnaires used to evaluate the condition of patients with osteoarthritis of the hip and knee. It assesses the pain, joint stiffness, physical, social and emotional function of a person with osteoarthritis. A reduced version of WOMAC has been validated and published by Whitehouse et al (2003) and will be used in this study.

Euro-Qol (EQ-5D-3L): The EQ-5D-3L 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 3 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).

Medical History Review: For participants continuing on in the extension study, details of any significant medical events that occur from the end of the 12 month study period to the signing of the extension study consent form will be captured as medical history in the extension study. This will ensure no adverse event data will be missed between termination from the ShapeNZRCT-10 study and re-enrolment into the Extension study.

12.0 STATISTICAL METHODS

12.1 Sample Size Justification

The New Zealand National Joint Registry reported a mean Oxford Knee Score of 37.05 (with a standard deviation of 8.30) at 6 months following total knee arthroplasty, using mostly conventional instruments (NZOA New Zealand Joint Registry, 2010). The registry also reports the following scoring categories: Excellent >41, Good 34-41, Fair 27-33, and Poor <27.

Kamat et al. (2009) undertook a study comparing the clinical outcomes of manual versus computer-assisted surgery instrumentations systems. A 5-point change in Oxford Knee Scores at a post-operative period of 6 months was determined to be a clinically meaningful difference.

A minimum of 45 patients per group are required, based on an improvement from 37 (mean Oxford Knee Score reported in the New Zealand registry) to 42 (scoring category of excellent), with 80% power and significance level of 5%.

An additional 5 patients per group (10%) has been included into the target patient number to allow for loss to follow-up, bringing the target to 50 patients per group.

A maximum of 100 patients will be enrolled in the Extension Study.

12.2 Data Capture and Analysis

All data will be recorded on 2-part NCR paper Case Report Forms (CRFs). The surgeon will complete and sign forms at the time of completion. Original 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 6).

Any unclear or ambiguous data will be queried and all cleaned data will be entered into a database for tracking purposes.

The primary outcome data gathered from patients in each study group will be pooled and summarized.

For the primary objective of the study, the 95% confidence interval of the difference in total Oxford Knee Score improvement (at 12 months post-operative) between the Intervention Group and the Control Group will be computed. Two and five year data will be analysed as per the 12 month data.

For secondary objectives, independent two-sample t-test or Wilcoxon non-parametric rank-sum test will be used to compare the International Knee Society Score (IKSS), Forgotten Joint Score (FJS), WOMAC, EQ-5D and VAS Pain scores between the Intervention Group and the Control Group at all available visits. Please note that the test we intend on using will be dependent on the distribution of the data collected following appropriate normality testing. Adjustments will be made for multiple testing at each level.

Independent two-sample t-test or Wilcoxon non-parametric rank-sum test will also be used to compare cost-effectiveness and cost-utility between the Intervention Group and the Control Group. As mentioned above, this will also be dependent on the distribution of the data collected.

Adverse events will be tabulated separately and reviewed for any commonalities. Revision surgery data from the Extension Study will be compared to the revision rates reported in the National Joint Registry report at 2 years and 5 years. A cost benefit analysis will be undertaken with the use of data from the Australian Government Hospital Casemix Protocol Annual Report.

A formal interim analysis will take place following completion of the ShapeNZRCT-10 study (12 month visit). Additionally, formal interim analyses will take place following all participants' completion of the 2 year visit and again following completion of all participants' 5 year follow-up visits.

13.0 SELECTION CRITERIA FOR INVESTIGATORS/SITES

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

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

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 Completion Form.

16.0 QUALITY ASSURANCE OF DATA

Case Report Forms (CRFs) 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 CONCURRENT 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 total 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 any time, 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
- Death
- Unable to Return
- Unwilling to Return
- Concurrent Illness
- Lost to follow-up
- Re-operation of the affected knee joint, including revision of total knee replacement components
- 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 Completion Form will be completed for all participants who withdraw from the study.

17.3 Emergency Unblinding

In the case of an Adverse Event, a participant may require un-blinding of treatment allocation (E.g. if revision surgery is required, or total knee replacement required on the opposing limb). In such case, deemed appropriate by the Principal Investigator, the participant may be notified of their allocation by the Principal Investigator, or designee and immediate notification should be sent to the study Sponsor, including the date un-blinding occurred. If a patient is un-blinded they will be terminated 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 not performed and follow-up) 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 medically important event or reaction.

19.2 Reporting of Events

Adverse Events:

Any adverse event that occurs at any time point from the beginning of the surgical procedure until either the patient is terminated from the study, or 30 days post-completion, 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). 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 (MedSafe NZ) 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 and Governance approval to conduct this study.

20.2 Prior to Initiation of the Study

The Investigator must wait for written approval by their 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 to the Sponsor and to the Investigator's Ethics Committee.

20.4 Withdrawal of Ethics 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 investigation, each Investigator will submit an Ethics Close-Out Report on his/her part of 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 RESPONSIBILITES

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. Any significant results from interim analyses will be communicated to the Investigator/s and ethics committee/s and any required changes to the protocol (as a result of these analyses) will be submitted as protocol amendments to the reviewing ethics committee.

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 Trial 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 Trial 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 Trial Agreement, the Protocol, the requirements of any MedSafe NZ 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.

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. 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

Surgical Protocol: Triathlon® Knee System with OtisMed® ShapeMatch® Technology

APPENDIX 2

PrecisioN Knee 4.0 Operating Technique

APPENDIX 3

CT Scan Protocol

APPENDIX 4

Outcome Assessment Tools:

- **Oxford Knee Score**
- **International Knee Society Score (IKSS)**
- **Forgotten Joint Score (FJS)**
- **Western Ontario McMaster Osteoarthritis Index (WOMAC)**
- **EuroQol-5D (EQ-5D)**
- **Visual Analogue Scale Pain (VAS Pain)**

APPENDIX 5

Declaration of Helsinki

APPENDIX 6

***Guideline on the Regulation of Therapeutic Products in New Zealand*. Part 11: Good Clinical Research Practice and obtaining approval for clinical trials, version 1.3, November 2012**

APPENDIX 7

Good Clinical Practice: Consolidated Guideline, CMP/ICH/135/95