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Orthopaedics

Triathlon PSR Outcomes Study

CLINICAL PROTOCOL

A prospective, post-market, multi-center evaluation of the clinical outcomes of the Triathlon Total Knee System using the Triathlon PSR Tibial Insert

Sponsor:	*Stryker Orthopaedics* *325 Corporate Drive* *Mahwah, NJ 07430* *201-831-5000*
Study Product:	*Triathlon PSR Tibial Insert*
Protocol Number:	*103*
510(k) Clearance Number:	*190402*

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CONFIDENTIAL

Protocol Change History

Version	Description	Changed By
1	New	Ajay Rastogi
1.1	Synopsis – Study Device Introduction Section 3.2 – Additional Devices Appendix B	Ajay Rastogi

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List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
CFR	Code of Federal Regulations
CPTi	Commercially Pure Titanium
CSM	Clinical Study Manager
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	International Conference of Harmonization Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
PI	Principal Investigator
QOL	Quality of Life
ROM	Range of Motion
SAE	Serious Adverse Event
SC	Study Coordinator
SF-36	Short Form-36
TKA	Total Knee Arthroplasty
UADE	Unanticipated Adverse Device Effect
UHMWPE	Ultra High Molecular Weight Polyethylene

Study Synopsis

Title	A prospective, post-market, multi-center evaluation of the clinical outcomes of the Triathlon Total Knee System using the Triathlon PSR Tibial Insert
Short Title	Triathlon PSR Outcomes Study
Protocol Number	103
Phase	Post-market
Methodology	This study is a prospective, post-market, non-randomized evaluation of the change between the preoperative and postoperative SF-36 outcomes in a consecutive series of primary total knee arthroplasty (TKA) patients who meet the eligibility criteria and received the Triathlon Globalization Knee System.
Study Duration	• Enrollment period of 24 months • Follow-up of each primary cemented TKA case to 10 years • Approximate 12-year total duration
Number of Centers	2 - 8 centers
Hypothesis	The SF-36 physical scores at 2 years for subjects receiving a cemented Triathlon Total Knee with the Triathlon PSR insert is comparable with that of historical Triathlon PS cemented constructs.
Objectives	**Primary:** • To compare the SF-36 physical scores for subjects receiving a cemented Triathlon Total Knee with the Triathlon PSR insert to scores for subjects who received historical Triathlon PS cemented constructs at 2-years postoperative. **Secondary Objectives:** • To evaluate the change between the preoperative and postoperative EQ-5D scores. • To evaluate range of motion (ROM) at 2-years postoperative. • To evaluate the survivorship of the Triathlon PSR insert at 10-years postoperative.

Additional Data Collection	• Subject demographics and medical histories are collected (age, sex, primary diagnosis, BMI, comorbidities, medications used, smoking history, alcohol use, education level, employment status, confounding orthopedic problems, etc.). • 2011 KSS will be presented with respect to improvement from preoperative scores. • The Forgotten Joint Score (FJS) will be collected at 2-years postoperative. • Assessment of radiographic outcomes using Anteroposterior (AP), Mediolateral (ML) and Merchant radiographs. • A Follow-up Questionnaire is administered to assess patient satisfaction, pain, study device survivorship and capture adverse events (AEs). • Collection and evaluation of device related AEs and unanticipated adverse device effects (UADEs).
Statistical Methodology	**Primary Objective:** • The mean SF-36 physical score at 2-years postoperative will be compared to 47.3 (the reference score from the historical control) with a non-inferiority margin of 2.5 points. • A two sided 90% confidence interval will be computed for the mean SF-36 score. If the lower bound is greater than 44.8, the non-inferiority hypothesis holds. **Secondary Objectives:** • The change of EQ-5D from preoperative to postoperative will be compared using a paired t-test. • The mean ROM at 2-years postoperative will be compared to the reference value from the historical control (124 degrees) with an error margin of 5 degrees. A TOST (two one-sided test) will be used to test the difference. • A Kaplan-Meier survival curve for all-cause revision/removals will of the Triathlon PSR insert will be displayed at 10-years postoperative. The survival rate will also be presented with a two-sided 95% confidence interval.
Number of Cases	A total of 250 cases (knees) will be enrolled in the study. Cases must receive the appropriate study device to count toward enrollment.

Study Device	Required Components: • Triathlon PSR Insert (X3 EtO) Compatible Stryker tibial baseplates, femoral components, and patellar components must be used in accordance with the applicable Instructions for Use and Surgical Technique(s). All components must be cemented with respect to the bone. Additionally, a variety of compatible Triathlon device accessories may be used, as indicated in the surgical protocol.

Inclusion/Exclusion Criteria	Inclusions: A. Patient has signed an IRB/EC approved; study specific Informed Patient Consent Form. B. Patient is a male or non-pregnant female, skeletally mature, age 18-75 years at time of study device implantation. C. Patient has a diagnosis of Non-Inflammatory Degenerative Joint Disease (NIDJD). D. Patient is a candidate for primary cemented total knee replacement. E. Patient is willing and able to comply with postoperative scheduled clinical and radiographic evaluations and rehabilitation. Exclusions: 1. Patient has a Body Mass Index (BMI) > 45. 2. Patient is already participating in the study for a contralateral total knee replacement. 3. Patient has a diagnosis of avascular necrosis or inflammatory arthritis. 4. Patient has an active or suspected latent infection in or about the affected knee joint at time of study device implantation. 5. Patient has any mental or neuromuscular disorder which would create an unacceptable risk of prosthesis instability, prosthesis fixation failure, or complications in postoperative care. 6. Patient has a compromised bone stock which cannot provide adequate support to the prosthesis. 7. Patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements (e.g. > 30 days). 8. Patient is diagnosed with lumbar radicular pain. 9. Patient has severe instability of the knee joint secondary to the absence of collateral ligament integrity and function. 10. Patient has a known sensitivity to device materials. 11. Patient is a prisoner.
Reference Therapy	Reference Control: Triathlon PS Cemented Femur with PS Insert (X3 and N2Vac), Triathlon Primary Cemented Baseplate, and Triathlon Patellar Component (X3 and N2Vac) ClinicalTrials.gov Identifier: NCT00957021

Evaluation Schedule

Evaluation	Preop X-rays (-1 yr) CRFs (-4 mos)	Intraop	6 wks (± 3 wks)	1 yr (± 2 mos)	2 yrs (± 2 mos)	3 yrs (± 3 mos)	4 yrs (± 4 mos)	5 yrs (± 4 mos)	Annually 6, 7, 8, 9 yrs (± 4 mos)	10 yrs (± 4 mos)
Inclusion/ Exclusion	X									
Demographics & Medical History	X									
Surgical Details		X								
Preoperative KSS	X									
Postoperative KSS			X	X	X			X		X
FJS					X					
SF-36	X		X	X	X	X	X	X		X
EQ-5D	X		X	X	X	X	X	X	X	X
Radiographs: AP/ML/Merchant View	X		X	X	X			X		X
Follow-up Questionnaire						X	X		X	

X: Evaluation is required for all cases.

KSS: The 2011 KSS is a standardized instrument with both patient-reported outcomes and surgeon completed sections that evaluate function, satisfaction, expectations and range of motion.
FJS: The FJS is a 12-item questionnaire assessing a patient's ability to forget his/her artificial joint in everyday life.
SF-36: The SF-36 is a standardized 36 item patient reported outcome questionnaire that evaluates general health and well-being.
EQ-5D: The EQ-5D is a standardized instrument for use as a measure of health outcome.
Follow-up Questionnaire: The Follow-up Questionnaire is a short patient questionnaire intended to provide information on patient satisfaction, pain, study device survivorship and AEs.
AP View: Radiographic view of the knee containing the femoral component, medial and lateral femoral epicondyles, and tibial component.
ML View: Radiographic view of the knee containing the patella, patellar component, and overlapping posterior condyles of the femoral and tibial component.
Merchant View: Radiographic view of the knee containing the articular surface of the patella and femur.

1 Introduction

This document is a protocol for a human research study. This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) Standards, Health Insurance Portability and Accountability Act (HIPAA) requirements, applicable Food and Drug Administration (FDA; 21 Code of Federal Regulations (CFR)), European, and International Organization for Standardization (ISO) regulations (ISO 14155).

1.1 Background

Primary total knee arthroplasty (TKA) has consistently shown to reliably relieve pain and improve function for patients suffering from end-stage knee arthritis.[1]

The Triathlon Knee system is designed to meet patients' reasonable expectations for patient satisfaction and return to function. As a next-generation knee replacement, the Triathlon Knee System closely mimics natural knee motion providing mobility with stability through or exceeding 150° of flexion[2]. The Triathlon design criteria are realized through component features including an anatomic, deep flexion radius, flared posterior condyles, a patented Rotary Arc and an anatomic patellofemoral track.

Studies of kinematics and biomechanics have identified a constant radius in natural knee motion centered about the transepicondylar axis[3,4,5]. The Triathlon Knee System is the first of its kind with a patented anatomic radius. Centering the anatomic radius about the transepicondylar axis provides ligament isometry, not only in full extension and 90° of flexion, but through the entire range of motion. The anatomic radius is designed to mimic natural knee motion, enhancing stability and mobility in activities such as descending and ascending stairs or any similar activity requiring stability at deep flexion angles.

With the number of patients receiving TKA rising annually, it has become increasingly important to accommodate cultural needs to achieve increased rotation in deep flexion for safe, deep knee bending. Posterior-stabilized (PS) implants have been shown to allow for higher flexion than cruciate-retaining (CR) implants making them better candidates to support the desired range of motion[6].

Axial rotation is an important consideration when looking to develop safe, high flexion implants. Natural axial rotation is approximately 30° through 120° of flexion. Replicating this degree of axial rotation in high-flexion implants is important in supporting the extensor mechanism at deep flexion and maximizing range of motion[7].

The Triathlon (PSR) tibial insert has been designed to accommodate the need for deep knee bending by reducing rotational constraint in deep flexion. The insert maintains key Triathlon PS design features including the post size and location, 45° tibial post-femoral cam engagement, Rotary Arc & Sagittal profile, and 10°-110° single radius flexion. The posterior reduction of the PSR insert allows the knee to better replicate the degree of normal axial rotation during deep knee bending. The Triathlon PSR insert is cleared for use under K190402. See **Appendix A** for clearance letters.

2 Clinical Study Plan

2.1 Study Design

A prospective, post-market, multi-center design will be employed. Radiographs will be assessed by an independent reviewer.

2.2 Study Centers

Cases will be enrolled at two to eight centers. There is no maximum limit to the number of cases that a center may enroll. In the event that a center far exceeds enrollment at other centers, Stryker may ask the center to cease enrollment so as not to skew the data. All participating centers will comply with the federal regulations regarding patient informed consent and Institutional Review Board (IRB) or Ethics Committee (EC) approval. Non-compliance of a study center may result in termination of the center's participation in the study.

2.3 Number of Subjects

Cases will be enrolled until at least 250 cases have received the Triathlon Total Knee System with the Triathlon PSR insert.

3 Device Description

3.1 Study Device

All cases in this post-market study will receive a Triathlon PSR insert.

The Triathlon PSR insert is intended to be used as a component in primary TKAs receiving a Triathlon Total Knee System. Fabricated from X3 ultra-high molecular weight polyethylene (UHMWPE), the insert is designed to reduce rotation constraint at deep flexion. The insert must be used with a compatible Triathlon baseplate, PS femoral component, and patellar component. For the purposes of the study, all components must be cemented with respect to the bone.

The Triathlon PSR insert is available in 9 sizes (Size 0-8) and 8 thicknesses (9, 10, 11, 12, 14, 16, 19, and 22 mm). Only Sizes 1-8 will be used in this study. All Triathlon PSR inserts will have a catalog number with the following format:

8532-G-XXX-E

The full listing of permissible Triathlon PSR catalog numbers may be found in **Appendix B**.

3.2 Additional Devices

The following **Stryker compatible** devices are to be used, according to this study protocol:

Table 1: Acceptable Additional Devices

Required Additional Components	
5515-F-XXX	Triathlon PS Cemented Femur
5520-B-XXX	Triathlon Primary Cemented Tibial Baseplate
5521-B-XXX	Triathlon Universal Tibial Baseplate
5550-G-XXX	Triathlon Patellar Component, Symmetric (X3)
5550-G-XXX-E	Triathlon Patellar Component, Symmetric (X3 EtO)
5550-L-XXX	Triathlon Patellar Component, Symmetric (N2Vac)
5551-G-XXX	Triathlon Patellar Component, Asymmetric (X3)
5551-G-XXX-E	Triathlon Patellar Component, Asymmetric (X3 EtO)
5551-L-XXX	Triathlon Patellar Component, Asymmetric (N2Vac)

Any on-label, compatible accessories may also be used. This includes, but is not limited to:

Table 2: Acceptable Accessory Devices

Acceptable Additional Components		
5575-X-000	Triathlon Femoral Distal Fixation Pegs	
5540-A-YYY	Triathlon Femoral Distal Augment & Locking Screws	5 mm
5541-A-YYY		10 mm
5542-A-YYY		15 mm
5543-A-Y00	Triathlon Femoral Posterior Augment & Locking Screws	5 mm
5544-A-Y00		10 mm
5545-A-YYY	Triathlon Tibial Augment	5 mm
5546-A-YYY		10 mm
5549-A-1YY	Triathlon Tibial Cone Augment	Symmetric
5549-A-2YY		Asymmetric
5560-S-YYY	Triathlon Cemented Stem	
5565-S-0YY	Triathlon Fluted Stem	100 mm
5566-S-0YY		150 mm
5570-S-0Y0	Triathlon Offset Adaptor	
5571-S-0YY	Triathlon Stem Extender	

The compatible Stryker components are listed in the surgical protocol and **Appendix B**.

In the case of any uncertainty regarding device compatibility, the current version of the Triathlon PS surgical protocol should be reviewed.

4 Study Procedures

4.1 Subject Recruitment and Screening

Patients will be recruited at the study centers during preoperative visits through normal referral patterns. Advertising for the study at each center will be at the discretion of the investigator. All handouts, brochures, advertisements, etc. must be approved by the IRB/EC prior to the dissemination of any recruitment materials to potential subjects.

During the preoperative visit, patients that are possible candidates for this study will be screened to determine if they meet the inclusion/exclusion criteria. If the patient is a candidate, the investigator will propose participation in the study to the patient, according to GCP guidelines. Patients must sign an IRB/EC approved Informed Patient Consent Form prior to participation in the study, as well as prior to any data collection.

4.2 Patient Informed Consent and Guidelines

All patients for this study will be provided an Informed Patient Consent Form describing this study and providing sufficient information for them to make an informed decision about their

participation. The Informed Patient Consent Form must contain all elements required by the FDA under 21 CFR Part 50, in addition to any other elements required by state, local and institutional policies. For international sites, the applicable country regulations are required. See **Appendix C** for a copy of the Model Informed Patient Consent. This will be submitted with the protocol for review and approval by the IRB/EC for the study. All patients must provide written consent after having had adequate time to consider their participation in the study. The formal consent of a patient, using the IRB/EC approved Informed Patient Consent Form, must be obtained before that patient is submitted to any protocol related procedures that are not part of normal care. Written documentation of consent must be provided on the Informed Patient Consent Form's signature page in addition to a note in the patient medical records indicating the date that consent was obtained. The investigator-designated research professional obtaining the consent must also sign this Informed Patient Consent Form. The patient or his/her legal representative should receive a signed copy of the Informed Patient Consent Form, according to GCP guidelines.

The procedure for obtaining informed consent is outlined below:

- Use a current IRB/EC approved copy of the Informed Patient Consent Form.
- Review thoroughly with the patient, allowing adequate time to consider participation in the study and ask questions, before having them sign.
- After the patient has consented to the procedures, ensure he/she signs and dates the Informed Patient Consent Form.
- The person obtaining consent also signs and dates the signature page.
- Provide a copy of the signed Informed Patient Consent Form to the patient.
- If required, provide the hospital with a copy of the signed Informed Patient Consent Form.
- Maintain the signed original in the patient's study chart.

4.3 Early Withdrawal of Subjects

When and How to Withdraw Subjects

In the event that the subject is discontinued by the investigative center prior to the final study evaluation, the subject will be notified by the center that he/she is no longer in the study and a Study Termination eCRF will be completed.

The following is a list of reasons for which subjects may be withdrawn and the date of termination that should be used on the Study Termination eCRF in each situation. This list is not all inclusive:

Termination Reason	**Date of Termination**
Death	Date of death
Investigative center termination	Date of study close-out visit
Lost to follow-up	Date Stryker termination approval given
Voluntary withdrawal	Date subject notified center of withdrawal
Revision/removal of study device	Date of revision/removal procedure
Study device not implanted	Date of surgery
Surgery not performed	Date Stryker termination approval given

At the time of study surgery, it is required that the following components are implanted to be included in the analysis:

- Triathlon PSR Tibial Insert
- Compatible Triathlon Tibial Baseplate
- Compatible Triathlon PS Femoral Component
- Compatible Patellar Component

All components must be cemented with respect to the bone.

Exchange of the Triathlon PSR Tibial Insert for any reason constitutes a failure and study termination for the subject.

If revision of any other component occurs during the study, the event does not constitute a failure or study termination.

If the subject fails to return for his/her follow-up appointments, every effort should be made to contact the subject to assess his/her health status. If, after attempting to contact the subject through three documented phone calls and a certified letter, the subject still does not respond, he/she will be considered lost to follow-up. A Study Termination eCRF will be completed **only after notifying Stryker of the subject's status** and **being given approval to terminate**.

In the event a subject does not have surgery, Stryker should be contacted to discuss if/when the surgery will be rescheduled. Preoperative data must be current within 4 months of the study surgery and will need to be re-collected if the surgery is rescheduled more than 4 months from the initial data collection. If the surgery is not to be rescheduled or if the subject is no longer

considered an appropriate study candidate, a Study Termination eCRF may be completed **only after notifying Stryker of the subject's status** and after Stryker **has given approval to terminate**.

When a subject completes the study according to protocol at the final study evaluation, a Study Termination eCRF will be completed.

5 Study Details

5.1 Study Objectives and Evaluation Schedule

The primary and secondary study objectives, as well as additional data collection are listed in Objectives and Additional Data Collection sections of the Study Synopsis (pages 8 and 9) For the evaluation schedule, please reference page 12.

5.2 Radiographic Outcomes

Radiographs will be taken and collected in the anteroposterior (AP), mediolateral (ML), and merchant views for the preoperative, 6-week, 1-, 2-, 5, and 10-year intervals. The suggested radiographic technique for the views required is included in **Appendix D.**

Radiographs will be evaluated by an independent reviewer throughout the course of the study. Parameters for radiographic failures will follow the guidelines that have been set by the Knee Society[8]. Radiographic analysis of the tibial component will employ seven zones (Zone 1 – Zone 7) in the AP view and three zones (Zone 1 – Zone 3) in the lateral view. Radiographic analysis of the femoral component will employ seven zones (Zone 1 - Zone 7) in the lateral view. Radiographic analysis of the patellar component will employ five zones (Zone 1 – Zone 5) in the merchant view. Numerous parameters will be reviewed including radiolucency, gaps and subsidence. Radiolucency in at least 50% of a zone and measuring at least 1 mm in width is defined as radiolucency present. Subsidence is defined as settling of the prosthetic component in bone and, for this study, is measured by looking at the change in position of the tibial baseplate with reference to a bony landmark (usually the very margin of the tibia) between visit

intervals. Cases that present with tibial baseplate subsidence of greater than 5 mm or at least 2 mm radiolucencies in all zones within a single view will be considered radiographic failures.

6 Adverse Events

6.1 Reporting of Adverse Events

The AE reporting requirements for this study are as follows:

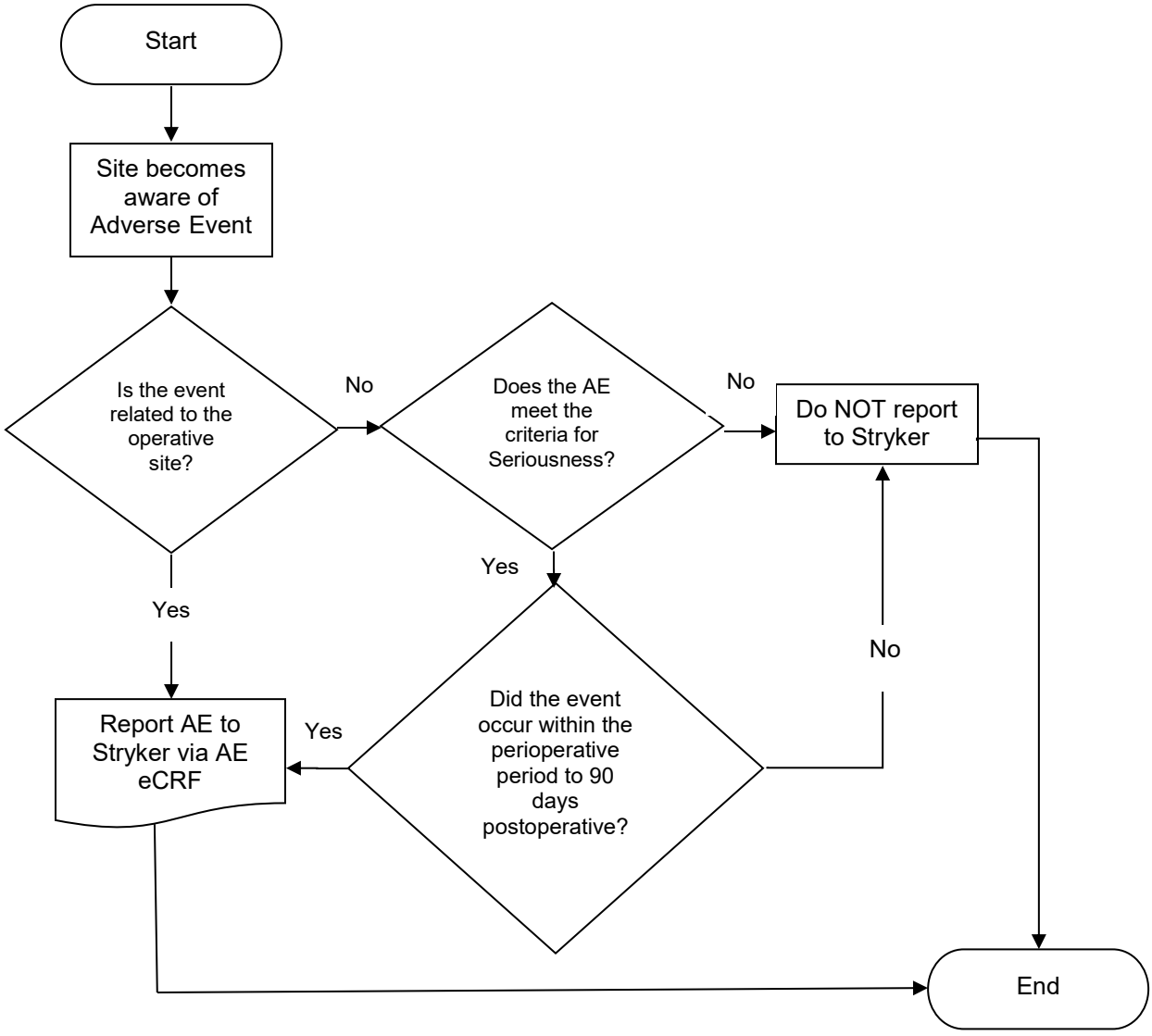
- All AEs that meet the definition of serious (see page 22) and occur within the perioperative period (intraoperative to hospital discharge) to 90 days postoperative
- All AEs related to the operative site, regardless of seriousness or time of occurrence

On postoperative functional evaluations, investigators and SCs will be prompted to question subjects as to whether they have seen a doctor for any reason, been hospitalized for any reason or have a current impediment to their function.

For the 6-, 7-, 8-, 9-year intervals, only a Follow-up Questionnaire will be administered. SCs will be responsible for following up with the subjects regarding any questionable responses received on the Follow-up Questionnaire. If it is determined upon this further investigation that a protocol-defined AE has occurred, the SC will be responsible for completing an AE eCRF, submitting the event to Stryker, and reporting the event to the IRB as required.

The following decision tree facilitates identification of AEs for which reporting is required under this study protocol:

Figure 1. Adverse Event Decision Tree



General Physical Examination Findings

At screening for inclusion into the study, any clinically significant abnormality should be recorded as a preexisting condition and reported on the Demographics eCRF. From the time of consent forward, any new clinically significant findings or abnormalities that meet the definition of a protocol defined AE must also be recorded and documented as an AE.

Adverse Event Reporting Period

The study period during which AEs must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. The start of study procedures is considered to be the point of consent. Any AEs which fit the protocol defined reportable events must be reported from the time of consent until study completion.

At each contact with the subject the investigator must seek information on AEs by specific questioning and, as appropriate, by examination. Information on protocol defined AEs should be recorded immediately in the source document and also in the appropriate AE module of the eCRF. All clearly related signs, symptoms and abnormal diagnostic procedure results should be recorded in the source document and grouped under one diagnosis, as appropriate. The clinical course of each event should be followed until resolution or until it is determined at the end of the study that the AE will not resolve.

All operative site events occurring at any time as well as all serious adverse events (SAEs) occurring within the perioperative period to 90 days postoperative will be collected and compared to published data. It is expected that the AE rates reported for the Triathlon Total Knee with the Triathlon PSR insert will be comparable to those for historical Triathlon PS cemented constructs.

6.2 General Adverse Event Definitions

Following is a list of general AE definitions. For the purposes of this study, only SAEs occurring within the perioperative period to 90 days postoperative, excluding elective procedures, as well as all AEs related to the operative site should be reported.

Adverse Event

An **AE** is any untoward medical occurrence in a clinical investigation subject, which changes the medical baseline of the subject. An AE can be an unfavorable and unintended sign, symptom or

disease, whether or not related to the study device (AEs may also be referred to as complications). See **Section 6.1, Reporting of Adverse Events**, for the AE reporting requirements for this study.

Anticipated Adverse Event

An **anticipated AE** is an AE, of which the nature, severity or degree of incidence is known and identified in applicable product labeling, published literature or the study protocol. The list of anticipated events is provided in **Section 11, Risk/Benefit Assessment**.

Serious Adverse Event

A **SAE** meets one or more of the following definitions:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in the following:
    - A life-threatening illness or injury
    - A permanent impairment of a body structure or a body function
    - An in-patient or prolonged hospitalization
    - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to foetal distress, foetal death or a congenital abnormality or birth defect

Adverse Device Effect

An **adverse device effect** (ADE) is a negative change in the subject's health that may have been caused by, or associated with, the use of the device.

Unanticipated Adverse Device Effect

An **unanticipated adverse device effect** (UADE) is any serious adverse effect on health, safety or any life-threatening problem or death caused by, or associated with, a device if that effect is a problem or death not previously identified in nature, severity or degree of incidence, or any other unanticipated serious problem associated with a device and related to the rights, safety or welfare of subjects.

6.3 Study Sponsor Notification by Investigator

Of reportable AEs, certain events must be submitted to Stryker within 24 hours for timely notification:

Adverse events that require time sensitive reporting:

An adverse event should be reported to Stryker Clinical Research either by telephone/fax/email **within 24 hours of the site becoming aware of the event if any of the following apply:**

- The AE occurs intraoperatively or is related to the surgical procedure.
- The AE is considered by the investigator to be device related or if the investigator is uncertain regarding the device related assessment;
- The AE required a reoperation of the study knee or a revision of any study knee components.

At the time of the initial report, the following information should be provided:

• Subject number • A description of the event • Date of onset • Current status	• Whether study treatment was discontinued • Investigator assessment of the association between the event and the study treatment

An AE eCRF for an AE meeting the criteria above should be completed within 24 hours of the investigative center's awareness, and the de-identified source documentation should be submitted to Stryker within 24 hours of the investigative center's awareness. These reports will be evaluated by Stryker to determine if a Product Inquiry (PI) is required.

It is recommended that all other reportable AEs are submitted through eCRF entry within 2 weeks.

6.3.1 Ethics Committee/Institutional Review Board Notification by Investigator

Reports of AEs (including follow-up information) must be submitted to the EC or IRB according to their specific requirements. Copies of each report and documentation of EC/IRB notification and receipt will be kept with the investigator's study files.

6.3.2 Device Retrieval Process

If the study device is removed for any reason, Stryker may retrieve the Triathlon PSR Insert and/or adjacent tissues for analysis to help characterize potential device-related complications. In the event that the Triathlon PSR Insert is removed from a study subject,

the procedure outlined in the Retrieved Implant Analysis Protocol (**Appendix E**) should be followed, as allowed by the hospital and institution. In addition:

1. When revision of a study subject is scheduled, the study coordinator (SC) should contact the Clinical Study Manager (CSM) or other Stryker Clinical Research personnel assigned to the project, as soon as possible.
2. Stryker Clinical Research will send a retrieval container to the SC.
3. After the device is explanted, the SC or an identified Stryker field representative will retrieve the device and place it in the retrieval container, following the instructions in **Appendix E**.
4. The SC, an identified field representative or Stryker Clinical Research will complete a Product Inquiry (PI).
5. If not completed by Stryker Clinical Research, the PI should be emailed to Stryker Product Surveillance at soprodexreports@stryker.com, as well as to the Clinical Research email addresses listed on the Sponsor Contact Sheet.
6. The PI should be attached to the retrieval container and sent to Product Surveillance. A de-identified operative report should be included, when available.
7. Stryker Clinical Research will follow up with Product Surveillance to obtain a PI number.
8. A summary of results will be provided to the investigator upon his/her request.

6.4 Recording of Adverse Events

All protocol defined AEs occurring during the study period must be recorded; this includes events that occur between visit intervals. The clinical course of each event should be followed until resolution or stabilization.

6.5 Medical Monitoring

It is the responsibility of the investigator to oversee the safety of the study at his/her center. This safety monitoring will include careful assessment and appropriate reporting of AEs, as previously noted. Stryker will conduct formal investigations via the Product Surveillance Department of those AEs which are submitted through our PI System.

7 Data Management

7.1 Database

Data will be collected at each center and entered into Stryker's Electronic Data Capture (EDC) system. The system can be accessed remotely by each investigative center and the data entered will be managed by Stryker. Subject data will be processed and monitored according to the protocol schedule by Stryker or Stryker representatives. Draft specifications to support eCRFs and electronic radiographic evaluation forms are provided in **Appendices F and G**, respectively.

7.2 Confidentiality

This study will comply with the 2002 HIPAA privacy rule. As such, Stryker will only collect that information which is necessary to support the objectives of the clinical study. Stryker will take precautions to ensure that data received is as de-identified as possible. In the case that some identified information is received, Stryker will ensure that any identifying information is not reported. Study subjects will authorize Stryker to use their health information in support of the clinical study during the informed consent process. Should a subject choose to withdraw authorization, Stryker may use data collected prior to the withdrawal of authorization.

7.3 Source Documents

Source data include all information, original records of clinical findings, observations or other activities in a clinical study necessary for evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, study worksheets, laboratory notes, memoranda, subject questionnaires, pharmacy dispensing records, recorded data from automated instruments, radiographs, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

All data points collected during preoperative and follow-up visits must be documented in the subject's chart. This includes range of motion values, pain and function as well as AEs and additional comments. The informed consent process should also be documented in the patient chart. Monitors, defined further in **Section 9**, will be comparing the eCRFs against source documents for accuracy. The monitors will seek to draw a reference between each data point on the eCRF and the subject's chart. Thus, one cannot derive pain, ROM or function based on a chart note that reads "Patient doing well." Every effort should be made to ensure complete source documentation.

Centers are required to create a source documentation plan including any applicable source documentation worksheets prior to enrollment.

7.4 Electronic Case Report Forms

The study eCRFs are the primary data collection instrument for the study. All data requested on the eCRF must be documented. All missing data must be explained. It is expected that eCRFs be completed and that any forms requiring signature are electronically signed by the investigator within 2 weeks of the evaluation date.

7.5 Data Queries

If errors or omissions are noted by Stryker upon review of the data entered into the eCRFs, a query will be sent to the center within the EDC system. Queries should be answered in a clear and comprehensible manner.

7.6 Protocol Deviations

Any major deviation from this protocol will be recorded by the Sponsor and must be reported to the EC/IRB by the investigational site according to their reporting procedures. Major protocol deviations for this study may include the following; this list may not be all-inclusive:

- Informed consent deviations, including but not limited to:
    - Study procedures performed prior to informed consent
    - Incorrect informed consent version used
- Patient enrolled does not meet the inclusion/exclusion criteria
- Protocol specified study component(s) not implanted
- Visit deviations, including:
    - Unavailable primary endpoint

If the center anticipates a possible protocol deviation, the investigator or SC should contact Stryker for guidance.

7.7 Records Retention

It is the investigator's responsibility to retain study essential documents for 2 years after the date of the final report, or 2 years after the date of investigative center termination. These documents should be retained for a longer period if required by an agreement with Stryker.

8 Statistical Plan

8.1 Study Objectives

8.1.1 Primary Objective Analysis

The primary hypothesis to be tested will be that the mean SF-36 Physical Score (PCS) at 2-years postoperative with a cemented Triathlon Total Knee with the Triathlon PSR Insert is not worse than 47.3 with a non-inferiority margin of 2.5 points. That is, the following hypothesis will be tested:

$$H0: \mu <= 47.3 - 2.5 \quad vs \quad HA: \mu > 47.3 - 2.5$$

Here, μ is the mean SF36 PCS at 2-years postoperative with a cemented Triathlon Total Knee with the Triathlon PSR insert. The reference value of 47.3 was derived from Triathlon PS study where subjects received a cemented Triathlon PS Total Knee with the PS Insert. (NCT00957021).

A 90% two-sided confidence interval (CI) will be computed for the mean SF36 PCS at 2-years postoperative. If the lower bound of the CI is greater than 44.8, then the non-inferiority holds. If the lower bound of the CI is greater than 47.3, then the mean SF36 PCS at 2-years postoperative is superior to 47.3.

8.1.2 Secondary Objective Analyses

The Kaplan-Meier survival curve of all-cause revision and removal of the Triathlon PSR insert will be displayed using SAS/PROC LIFETEST at 10-years postoperative. The survival rate at 10 years will be presented with a 95% CI.

The ROM at 2 years will be compared with 124 degrees, as derived from Triathlon PS study, using an equivalence margin of 5 degrees. A TOST (two one-sided test) will be used with SAS/PROC TTEST to test the difference.

The change between the preoperative and postoperative EQ-5D TTO scores will be tested with Paired T-tests.

The analysis for the additional data collected is in **Section 8.4.1**.

8.2 Safety

8.2.1 Safety Parameters

Safety parameters include all protocol-defined adverse events as well as all-cause revision and/or removal of any component of the Triathlon Total Knee with the Triathlon PSR Insert. For details regarding protocol-defined adverse events, see **Section 6.1**.

8.2.2 Safety Analyses

The frequency and percentage of all protocol-defined adverse events will be tabulated. All protocol-defined adverse events will be tabulated, and a 95% CI will be presented. For details regarding protocol-defined adverse events, see **Section 6.1**.

8.3 Missing Data

No missing data will be imputed.

8.4 Statistical Methodology

8.4.1 Data Summary

Descriptive statistics will be computed for all baseline conditions and demographic parameters. That is, for continuous data, the N, mean, standard deviation, minimum value and maximum value will be computed. For categorical data, the frequency will be computed. The data will be presented by appropriate subgroups (e.g., center).

For all additional data collected that are not required for direct support of a study objective, data will be summarized according to visit. For parameters represented by continuous variables (e.g., BMI), the summaries will consist of the N, mean, standard deviation, minimum, and maximum values. For categorical variables (e.g., comorbidities), the frequency and percentage in each category will be presented.

Radiographic data will be presented for each visit interval at which radiographs are collected. The frequency and percentage of radiographic failures will also be presented accordingly.

Documentation of statistical analyses will be performed utilizing SAS® software version 9.3 or higher.

8.4.2 Sample Size Justification

Based on the Triathlon PS clinical study, it is reasonable to have a SF36 PCS reference value of 47.3 (with a standard deviation of 10.7) at 2-years postoperative. Two hundred cases are needed to have a power of 95% to detect that the mean SF36 PCS at 2-years postoperative is non-inferior to the reference value with a margin of 2.5 at 5% significance level. After factoring in a 20% lost to follow-up rate, a total of 250 cases will be needed.

8.4.3 Interim Analyses

No interim analysis is planned.

8.4.4 Analysis Population

Per Protocol Population:

The study population for analysis will include all non-censored subjects who received a cemented Triathlon Total Knee with the Triathlon PSR insert and are available for primary objective evaluation at the 2-year primary endpoint.

The primary and secondary objective analyses will be based on the per protocol population.

Safety Population:

The safety population will include all non-censored subjects who received a cemented Triathlon Total Knee with the Triathlon PSR insert.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

Monitors are persons employed by sponsors to review the conduct of clinical studies to assure that the clinical investigators abide by their obligations to conduct clinical studies properly. Proper monitoring ensures adequate protection of the rights of human subjects, the safety of subjects involved in a clinical investigation and the quality and integrity of data submitted as a result of the investigation.

Each investigational site conducting this study will be monitored at least once per year, with additional monitoring as necessary. The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or

quality assurance reviewer is given access to all study-related documents and study-related facilities, as applicable, and has adequate space to conduct the monitoring visit, when applicable. The monitor will review all source documents and compare them to the data contained in the eCRFs, in addition to performing a periodic review of regulatory documents such as EC/IRB approvals. The monitors will need the following:

- An area where they can review study data, when monitoring is conducted on site
- Access to eCRF data for all cases
- Access to source documentation
- Regulatory documents
- Time to discuss findings with the SC and the investigator

9.2 Auditing and Inspecting

A quality assurance audit is a form of review that provides additional confidence to the sponsor concerning the validity and accuracy of clinical study data that may be submitted to the FDA or for publication. The purpose of investigator audits is to ensure that the investigator has maintained all study information according to the sponsor's protocol and standard operating procedures and in compliance with FDA regulations.

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, Stryker and/or government regulatory bodies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities.

10 Publication Plan

It is anticipated that publication of the multi-center study results will be compiled and submitted to a peer-reviewed journal at the time the study cohort reaches 2 years and 10 years of follow-up. Early results with regard to surgical information and postoperative biomechanics may be published prior to the 2-year time point. Additional publication proposals may also be made by investigators at any time and will be considered.

This study will utilize the guidelines for authorship published by the International Committee of Medical Journal Editors (ICMJE). This guidance can be referenced at www.icmje.org.

At the completion of the study, each participating study investigator shall have independent publication privileges for his/her own center's results. These manuscripts and abstracts will be delayed until after the 2- and 10-year multi-center publications are submitted. Although Stryker will not be involved in coordinating these independent manuscripts, all publications of the data shall be submitted to Stryker for review prior to submission for publication. Stryker shall not edit or otherwise influence the publications other than to ensure that confidential information is not disclosed, that no off-label use of Stryker devices is promoted and that the data is accurately represented. Any publications resulting from this study must be submitted to Stryker for review at least 60 days prior to submission of publication.

11 Risk/Benefit Assessment

11.1 Risk Category

There are no additional risks associated with participating in this study over and above that of the primary TKA procedure.

11.2 Potential Risk

The study involves the routine assessment of a primary TKA procedure. The Triathlon PSR Tibial Insert has been cleared for use by the FDA, is CE certified, and will be used according to the labeling included in **Appendix H**. Breach of data privacy is a known risk. All study assessments, patient and physician evaluations as well as radiographs will be kept confidential and will comply with the HIPAA privacy rule.

While the expected life of TKA components is difficult to estimate, it is finite. These components are made of foreign materials, which are placed within the body for the potential restoration of mobility or reduction of pain. However, due to the many biological, mechanical and physiochemical factors which affect these devices but cannot be evaluated in vivo, the components cannot be expected to indefinitely withstand the activity level and loads of normal healthy bone. Surgeons should counsel patients against having unrealistic expectations about the lifetime of the device.

Risks associated with primary TKA include the following:

- Dislocation of the femoral, tibial, or patellar prosthesis can occur due to inappropriate patient activity, trauma or other biomechanical considerations.

- Loosening of total knee components can occur. Early mechanical loosening may result from inadequate initial fixation, latent infection, premature loading of the prosthesis, component malalignment or trauma. Late loosening may result from trauma, infection, biological complications including osteolysis, or mechanical problems, with the subsequent possibility of bone erosion and/or pain.

- Fatigue fracture of total knee components, including tibial, femoral and patellar components, has occurred in a small percentage of cases. Knee component fracture may result due to inadequate support of the component by the underlying bone or poor component fixation.

- Peripheral neuropathies, nerve damage, circulatory compromise and heterotopic bone formation may occur.

- Serious complications may be associated with any total joint replacement surgery. These complications include, but are not limited to: infection; genitourinary disorders; gastrointestinal disorders; vascular disorders, including thrombus; bronchopulmonary disorders, including emboli; myocardial infarction or death.

- With all implanted devices, asymptomatic, localized progressive bone resorption (osteolysis) may occur around the prosthetic components as a consequence of foreign-body reaction to the particulate matter of metal and UHMWPE. Particulate is generated by interaction between components as well as adhesion, abrasion and fatigue. Secondarily, particulates can be generated by third body wear. Osteolysis can lead to future complications, including loosening, necessitating the removal and replacement of prosthetic components.

- Wear of polyethylene components has occurred, and literature reports have associated its occurrence with bone resorption, loosening and infection.

- Soft tissue imbalance and/or laxity has been related to component malalignment, which may result in early wear and/or failure of the implant.

- Intraoperative fissure, fracture, or perforation of the femur or tibia can occur due to impaction of the component into the prepared femur or tibia. Postoperative femoral or tibial fracture can occur due to trauma, the presence of defects or poor bone stock.

- Asymptomatic, localized progressive bone resorption (osteolysis) may occur around the prosthetic components as a consequence of foreign-body reaction to the particulate matter of metal, UHMWPE and/or ceramic. Particulate is generated by interaction between components as well as adhesion, abrasion and fatigue. Secondarily, particulates can be generated by third body wear. Osteolysis can lead to future complications, including loosening, necessitating the removal and replacement of prosthetic components.

- Metal sensitivity reactions have been reported following joint replacement.

11.3 Expected Complications

Complications associated with TKA procedures, such as those performed with the study device, have been reported. These include the potential for but are not limited to: infection, genitourinary disorders, gastrointestinal disorders, vascular disorders, bronchopulmonary disorder, myocardial infarction, injury to the knee's neurovascular structures, loosening of the components, osteolysis, heterotopic bone formation, deep vein thrombosis, pulmonary embolism, metal sensitivity reactions, intraoperative or postoperative fracture of the femur, patella or tibia, and the need for re-operation, revision, arthrodesis of the involved joint, amputation of the limb and death. The safety analysis will include tabulation of AE rates as well as revision/removal rates.

11.4 Protection Against Risks

Subjects will be treated in the best medical judgment of the investigator, regardless of the study protocol. If an investigator must deviate from the written protocol to protect the health or wellbeing of the subject, this deviation will be promptly reported to both the EC/IRB and Stryker.

11.5 Potential Benefits to the Subject

There is no guarantee that subjects will personally benefit from inclusion in this study. Subjects may undergo more thorough screening and follow-up than non-study patients and may benefit from this increased surveillance. This study seeks to provide clinicians information about this device by comparing it to published results for other similar devices. Information gathered in this study may benefit others undergoing this procedure in the future.

12 Ethical Considerations

This study is to be conducted according to United States standards of GCPs and applicable government regulations including 21 CFR Parts 50 and 56 as well as 45 CFR Parts 160 and 164, as well as ISO 14155.

This protocol and any amendments will be submitted to a properly constituted independent EC/IRB for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Stryker before commencement of this study. The investigator may be asked to provide a list of EC/IRB members and their affiliates to Stryker, if available.

All patients considered for this study will be provided an Informed Patient Consent Form describing this study and providing sufficient information for patients to make an informed decision about their participation. This Informed Patient Consent Form must be modified to contain center specific information and submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a patient, using the EC/IRB approved Informed Patient Consent Form, must be obtained before that patient is submitted to any study procedure. This Informed Patient Consent Form must be signed by the patient or legally acceptable surrogate and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This study is financed by Stryker.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (e.g. patent ownership, royalties or financial gain greater than the maximum allowable by their institution) must have the conflict reviewed by their EC/IRB or a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by Stryker prior to participation in this study.

13.3 Subject Stipends or Payments

Subject attrition can occur for a variety of reasons, including a subject's loss of health insurance coverage. In a case where a patient has lost health insurance coverage and no other coverage is available, Stryker may, on a case-by-case basis, reimburse investigators for office visits and radiographic charges for subjects involved in this study in order to facilitate data retrieval. The physician or the office staff should contact the CSM prior to scheduling the subject to discuss this possibility and receive pre-approval. After receipt of the completed data forms, the physician must submit either evidence of coverage denial (e.g. explanation of benefits) or a letter explaining that the subject does not have insurance. Other visits, procedures and assessments done other than those specified in the protocol will not be reimbursed. Reimbursement may be provided under the following conditions:

- Study subjects lose insurance coverage after enrollment into the study
- An insurance carrier refuses to pay for a follow-up visit and/or radiographs
- An insurance carrier refuses to provide a subject referral to see the investigator for follow-up

Additionally at pre-determined study visit intervals, Stryker may reimburse subjects with a modest stipend for protocol-required data collection. This stipend system must be approved by the Institution's IRB prior to implementation and will be based upon individual IRB approval from each site.

14 References

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8. Ewald FC. The Knee Society Total Knee Arthroplasty Roentgenographic Evaluation and Scoring System. Clin Orthop and Relat Res. 1989; 248: 9-12.