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Orthopaedics

Triathlon TS Outcomes Study

CLINICAL PROTOCOL

A prospective, post-market, multi-center study of the outcomes of the Triathlon Total Stabilizer (TS) Total Knee System

Sponsor:	*Stryker Orthopaedics* *325 Corporate Drive* *Mahwah, NJ 07430* *201-831-5000*
Study Product:	*Triathlon TS Total Knee System*
Protocol Number:	*65*
510(k) Clearance Numbers:	*K072221 – October 15, 2007*

Version 2.0

Date: 3/27/2013

Protocol Change History

Version	Description	Changed By
A 8/3/2007	New	Rama Ramakrishnan
B 9/12/2007	Statistical analysis and sample size are included. Knee and Osteoarthritis Outcome Score (KOOS) is added.	Rama Ramakrishnan
C 10/29/2007	Modified all study design parameters, including but not limited to primary and secondary objectives, reference therapies, inclusion/exclusion criteria, and evaluation tools.	Diana F. Comarato
D 12/3/2007	Basis of primary objective changed to Knee Society Score (KSS). Modified non-inferiority statistical analysis and sample size included. Additional patient questionnaire included. Joint line (JL) guidelines modified. Entire protocol revised. Appendices created.	Diana F. Comarato
1.0 3/3/2008	Draft status removed.	Diana F. Comarato
2.0 3/27/2013	Removed trademark and service marks per current Intellectual Property guidelines.	Kristin L. Given

	Added clarification throughout that only cases implanted with the required study device will count toward the enrollment goal. Updated study devices and description to remove the unavailable Triathlon TS Extended Condyle Femoral Component and Triathlon TS Tibial Insert and include N2Vac tibial inserts and patellar components. Added Appendix I. Updated section 12.3 to remove references to outdated complication rate data.	

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List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ANCOVA	Analysis of Covariance
AP	Anteroposterior
BMI	Body Mass Index
CRF	Case Report Form
CSA	Clinical Study Associate
CSM	Clinical Study Manager
DCF	Data Clarification Form
EC	Ethics Committee
ECF	Extended Condyle Femur
FH	Fibular Head
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HSS	Hospital for Special Surgery
ICMJE	International Committee of Medical Journal Editors
IPP	Inferior Pole of the Patella
IRB	Institutional Review Board
JL	Joint Line
KOOS	Knee and Osteoarthritis Outcome Score
KSS	Knee Society Score
LEAS	Lower Extremity Activity Scale
ME	Medial Femoral Epicondyle
ML	Mediolateral
PER	Product Experience Report
PI	Primary Investigator
PMMA	Polymethylmethacrylate
PS	Posteriorly Stabilized
QOL	Quality of Life
ROM	Range of Motion
SAE	Serious Adverse Event
SC	Study Coordinator
SF-36	Short Form-36
TS	Total Stabilizer
TT	Tibial Tubercle
TKR	Total Knee Replacement
UADE	Unanticipated Adverse Device Effect
UHMWPE	Ultra High Molecular Weight Polyethylene

Study Synopsis

Title	A prospective, post-market, multi-center study of the outcomes of the Triathlon TS Total Knee System
Short Title	Triathlon TS Outcomes Study
Protocol Number	65
Phase	Post-market
Methodology	This study will be a prospective, non-randomized evaluation of the change between preoperative and postoperative outcomes for those receiving the Triathlon TS Total Knee System.
Study Duration	• Long term follow-up of each revision total knee replacement (TKR) case to 5 years • Anticipated enrollment period of 53 months • Approximate 10-year total duration
Study Center(s)	12
Hypothesis	The mean total KSS change is not 10% worse than, or is superior to, the expected change according to published revision TKR data, for cases implanted with the Triathlon TS Total Knee System as compared from preoperative to 2 years postoperative.

Objectives	Primary: • To evaluate the change in outcomes from the preoperative time point to 2 years postoperative in cases implanted with the Triathlon TS Total Knee System, with regard to both components of the KSS. Secondary: • To evaluate the effect of JL restoration on postoperative stability, anterior knee pain and functional performance. A subset of revision TKR cases will be analyzed by comparing between two groups: • Cases with JL restoration > 5 mm and cases with JL restoration ≤ 5 mm • To evaluate the change between preoperative and postoperative outcomes other than the KSS for the Triathlon TS Total Knee System group. • To review radiographic stability, revision rates and complications for those implanted with the Triathlon TS Total Knee System.
Number of Subjects	181 cases implanted with the Triathlon TS Total Knee System as required under this protocol

Diagnosis and Main Inclusion/Exclusion Criteria	Inclusions: A. Patient has signed an IRB approved, study specific Informed Patient Consent Form. B. Patient is a male or non-pregnant female age 18 years or older at time of study device implantation. C. Patient is a candidate for revision of all femoral and tibial components of a total knee replacement. D. Patient is willing and able to comply with postoperative scheduled clinical and radiographic evaluations and rehabilitation. Exclusions: E. Patient has a Body Mass Index (BMI) > 40. F. Patient has an active or suspected latent infection in or about the affected knee joint at time of study device implantation. G. Patient has a neuromuscular or neurosensory deficiency, which limits the ability to evaluate the safety and efficacy of the device. H. Patient is diagnosed with a systemic disease (e.g. Lupus Erythematosus) or a metabolic disorder (e.g. Paget's Disease) leading to progressive bone deterioration. I. Patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements (e.g. > 30 days). J. Patient has a failed unicondylar knee prosthesis. K. Patient has a known sensitivity to device materials. L. Patient is a prisoner.

Study Device	**Triathlon TS Total Knee System** Required Components: • Triathlon TS Femoral Component • Triathlon TS Plus Tibial Insert or Triathlon PS Tibial Insert • Triathlon TS Universal Tibial Baseplate The femoral component and tibial baseplate must be used in a cemented application. The subject's patellar component may or may not be revised based upon surgeon discretion. If revised, a Triathlon Patellar Component must be used, and in a cemented application. Additionally, a variety of Triathlon TS device accessories may be used.
Reference Therapy	Comparison of preoperative to postoperative outcomes, both within the study group and with respect to published revision TKR data.

Statistical Methodology	Primary: A one-sided 95% confidence interval of the total KSS change from preoperative to 2 years postoperative (2 years - preoperative) will be computed at 2 years postoperative. For the non-inferiority comparison, the lower bound of this confidence interval will be compared with 63 points (10% worse than the expected improvement). For the superiority comparison, the lower bound of this confidence interval will be compared with 70 points (the expected improvement). Secondary: An independent group t-test or a nonparametric test will be used to compare the secondary numerical parameters (e.g. KSS, HSS, KOOS) between the JL restoration subgroups at 1, 2 and 5 years postoperative; and a Chi-square test or Fisher's exact test will be used to compare the secondary categorical parameters (e.g. postoperative stability, anterior knee pain and functional performance) between the subgroups. In addition, a paired t-test or Wilcoxon rank sum test will be used to compare the change in outcomes other than the KSS from preoperative to 1, 2 and 5 years postoperative within the Triathlon TS Total Knee System group. The radiographic stability rates, adverse event (AE) rates and revision rates with 95% confidence intervals will be presented in tables.

Evaluation Schedule

Evaluation	Preoperative (4 months prior to surgery)	Intraoperative	6 weeks (± 2 weeks)	6 months (± 2 weeks)	1 year (± 2 months)	2 years (± 2 months)	5 years (± 2 months)
Inclusion/ Exclusion	X						
Demographics & Medical History	X						
Preoperative KSS	X						
Previous Implant Information		X					
Surgical Details		X					
Postoperative KSS			X		X	X	X
SF-36	X			X	X	X	X
KOOS	X			X	X	X	X
Hospital for Special Surgery (HSS) Patella Score	X			X	X	X	X
LEAS	X			X	X	X	X
Radiographs: Anteroposterior (AP), Mediolateral (ML) & Merchant (30° of flexion)	X		X		X	X	X

KSS: The KSS is a subjective outcomes tool completed by the investigator that measures function, pain, and motion.

SF-36: Short Form-36 (SF-36), is a 36 item patient questionnaire that evaluates general health and well being.

KOOS: The KOOS is a self-administered patient questionnaire that assesses pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life (QOL).

HSS Patella Score: The HSS Patella Score incorporates both subjective symptoms and objective data specific to the patellofemoral joint.

LEAS: The Lower Extremity Activity Scale (LEAS) is a self-administered patient evaluation designed to reflect patient activity.

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, associated Federal regulations, and all applicable research requirements.

1.1 Background

As the population ages, so does the incidence of arthritis and subsequent primary TKR. Frequency of revision for failed TKR increases as well, aimed at alleviating pain and improving function following time-dependent primary implant failure or complications such as infection and fracture.[1] The primary goals of revision TKR are to alleviate pain and provide the patient with stable, well-functioning TKR through optimal implant fixation and restoration of knee biomechanics. Appropriate TKR biomechanics are established through adequate flexion-extension gap balancing, proper mechanical and rotational alignment, proper patellofemoral mechanics and restoration of the JL.[2]

Revision TKR outcomes typically decline with each successive revision.[3] However, patient expectations of postoperative function, pain relief and adequate QOL may not be adjusted for the expected decline in functional results observed in revision TKR. Some long-term data exists to describe the effectiveness of revision TKR. Sheng et al.[4] performed a meta-analysis of publications on patient outcomes following revision TKR. Thirty-three studies with a total number of 1356 patients were included in this analysis, which reported increased function and motion compared to preoperative scores. The main indication for revision reported is aseptic loosening (55%). Other reasons include polyethylene wear (11%), instability (10%), infection (7%), progression of disease (4%), osteolysis (4%), bone fracture (4%), component failure (3%), stiffness (1%) and pain of unknown origin (1%). Instability can be caused by malposition of the JL, imbalance in flexion and extension gaps or incompetence of the posterior cruciate ligament.

There is little existing data reporting outcomes for a single type of revision TKR prosthesis, such as the Triathlon TS Total Knee System. To date, differences between various revision TKR implant systems are not reported in the scientific literature.[5] Long-term outcomes data among a new generation of revision TKR prostheses is needed.

In addition to improving patient outcomes, one of the challenges in revision TKR is restoration of the JL. Improper positioning of the JL has been shown to lead not only to instability but also to an increased incidence of anterior knee pain and decreased flexion.[6] Malposition may also lead to patellar infera and posterior soft tissue impingement by the femoral component. Mason et al.[7], in a study of six cadaver knees, investigated four anatomic landmarks for locating the JL during revision knee surgery – the medial femoral epicondyle (ME), the fibular head (FH), the tibial tubercle (TT), and the inferior pole of the patella (IPP). In this study, the distance between the ME and the JL showed very small patient-to-patient variability. As a result, it was concluded that the ME is a reliable and reproducible landmark for JL measurements.[8]

Additionally, Mahoney and Kinsey[9] retrospectively reviewed JL restoration and clinical outcomes in 22 consecutive femur revision cases. The authors used specialized instruments and were able to restore JL to within 2 mm of anatomic position in 12 of the 22 knees. Flexion and extension gap balancing and ME referencing were reliable methods of measuring and achieving proper position of the JL.

As a secondary objective, this outcomes study of the Triathlon TS Total Knee System will also examine the effect of JL restoration on a subset of revision TKR cases with a non-replaced contralateral knee at the time of study surgery. The effect will be evaluated by comparing between cases with JL restoration > 5 mm and cases with JL restoration ≤ 5 mm. As little as 5 mm of displacement from the JL can cause laxity in midflexion or tightness, even in a gap-balanced knee.[10]

For all cases, at the time of study surgery, surgeons will intraoperatively measure, in millimeters, the distance between the ME and the JL in full extension and in 90° of flexion. This measurement will be taken before removal of the previous implants as well as after implantation of the final Triathlon® TS Total Knee System.

Additionally, preoperative and postoperative measurements of JL will be taken from AP radiographs, as the distance from the proximal tip of the FH to the distal most aspect of the femoral component. When the contralateral knee is non-replaced, the measurement will be taken on both sides. These additional measurements will be obtained during independent radiographic review to eliminate interobserver and intraobserver error.

The protocol for measuring JL is referenced in Appendix A. Stability, anterior knee pain and the functional component of the KSS will be evaluated with respect to JL.

1.2 Study Device

The Triathlon TS Total Knee System has been developed as platform knee technology for Stryker Orthopaedics. The Triathlon TS Total Knee System, cleared for use under FDA 510(k) K072221, includes femoral components fabricated from cast cobalt-chromium-molybdenum alloy, distal and posterior femoral augments, fluted stems, stem extenders, offset adapters, tibial inserts fabricated from ultra high molecular weight polyethylene (UHMWPE) and a patellar component also made from UHMWPE. When mated with the Triathlon TS Universal Tibial Baseplate fabricated from cast cobalt-chrome-molybdenum alloy and tibial augments, these parts provide a total stabilizing knee replacement. The Triathlon TS Total Knee System features an anatomic radius and shortened posterior condyles. These features may allow patients to achieve a greater range of motion (ROM) and greater stability throughout their ROM. Data in support of these marketing claims will be collected in the Triathlon TS Outcomes Study.

1.3 Preclinical Data

The following bench tests were conducted on the Triathlon TS Total Knee System components:

Description of the test	**Report ID**
Static Shear	– RD-06-122
Femoral Stem Boss Fatigue	– RD-06-127
Femur Fatigue	– RD-06-126
Single Axis Fatigue	– RD-06-123
Varus/Valgus Constraint	– RD-06-121
Multi Axis Fatigue	– RD-06-120
Fluted Stem Fatigue	– RD-06-119
Range of Constraint	– RD-06-124 and RD-06-125

Copies of all test reports are available at Stryker Orthopaedics.

1.4 Clinical Data to Date

This study is the first prospective data collection on the Triathlon TS Total Knee System. To date, early data from this study have been presented at the 2012 meetings of the International

Congress for Joint Reconstruction and the Southern Orthopaedic Association. The abstract is summarized below.

Title	Authors	Summary
Anatomic Boss Position Decreases the Need for Offset in Revision Total Knee Arthroplasty	Hitt, Kirby; Stoker, Manoshi; Howard, Michael; Mittal, Yogesh and Heekin, David	Among 83 cases enrolled at 5 sites, 90.4% did not require a femoral offset; this is in contrast to previous reports that femoral offset adapters were needed in 55.4% of cases to achieve optimal joint line reconstruction. The authors concluded that the design of this system inherently reduced the need for use of the offset adapter in the majority of cases due to the anatomic boss position.

2 Study Objectives

2.1 Efficacy

2.1.1 Primary

The primary objective of this study will be to evaluate the change in outcomes from the preoperative time point to 2 years postoperative in cases implanted with the Triathlon TS Total Knee System, with regard to both components of the KSS. The change seen from preoperative to postoperative time points will be evaluated within the Triathlon TS group and will also be compared to published revision TKR data. It is expected that the change in the Triathlon TS group is non-inferior, or superior, to the published changes reported.

2.1.2 Secondary

The secondary objectives of this study will be to evaluate the effect of JL restoration on revision TKR with specific reference to effect on postoperative stability, anterior knee pain and functional performance at 2 and 5 years postoperatively. It is expected that the Triathlon® TS group with JL elevation > 5 mm is non-inferior to the Triathlon TS group with JL elevation ≤ 5 mm.

All outcomes other than the change in KSS, already analyzed as the primary objective, will be analyzed from preoperative to 1, 2 and 5 years postoperatively.

Additionally, the long-term performance of the Triathlon TS Total Knee System for revision TKR will be evaluated with regard to radiographic stability, revision rate and complications when reviewed against published data.

Clinical Outcome

Clinical outcomes will be evaluated via the total KSS, including pain, motion and function, preoperatively and at the 6-week, 1, 2 and 5-year visits.

Patient Outcomes

Four different tools will be used to assess patient health-related QOL preoperatively and at the 6-month, 1, 2 and 5-year visits.

The SF-36 is a 36 item patient questionnaire that evaluates general health and well being by measuring components of physical and mental health. The KOOS will be used to collect information specific to osteoarthritis outcomes and consists of six areas: symptoms, stiffness, pain, functions of daily living, sports and recreational activities and QOL.[11] The HSS Patella Score incorporates both subjective symptoms and objective data specific to the patellofemoral joint.[12] The LEAS is a tool that has recently been developed and validated to evaluate the level of patient activity.[13]

Radiographic Outcomes

Radiographs will be taken and collected in the AP, ML, and Merchant (30° of flexion) views for the preoperative, 6-week, 1, 2 and 5-year intervals. See Appendix B for the radiographic technique to be used.

Radiographs will be evaluated by an independent reviewer for radiolucency of all components, and subsidence for the tibial and femoral components of the Triathlon TS Total Knee System. JL measurements will also be taken according to Appendix A.

Patellar component positioning will be assessed to determine the presence of tilt and/or displacement. Parameters for radiographic failures will follow the guidelines that have been set by the Knee Society.[14] The scoring system for each of the three components is determined by measuring the width of the radiolucent lines for each of the zones in millimeters for each of the three components. The total widths are added for each zone for each of the three prostheses. The total produces a numerical score for each component. Failure is defined as a score of 10 or greater, regardless of symptoms. A migrating or shifting prosthesis, with or without the disappearance of radiolucent lines, should be considered as a possible or impending failure regardless of the score.

Performance Requirements

Radiographic analysis of the femoral component will employ seven zones (Zone 1 – Zone 7) in the ML view; analysis of the tibial component will employ three zones (Zone 1 – Zone 3) in the ML view and seven zones (Zone 1 – Zone 7) in the AP view; analysis of the patellar component will employ five zones (Zone 1 – Zone 5) in the Merchant (30° of flexion) view. 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 is related to the distance between fixed bony landmarks on the tibia and the prosthesis. It should be noted that Knee Society guidelines state that direct subsidence without angular movement cannot be detected because there is no reference point.[15]

Surgical Details

In order to promote efficiency in the operating room, the Triathlon Total Knee Instrumentation was consolidated, color coded and configured in modules that

correspond to the surgical procedure. To assess efficiency, measures of surgical time will be collected to support future improvements.

JL measurements will also be taken intraoperatively according to Appendix A. Investigators will measure, in millimeters, the distance between the ME and the JL. This measurement will be taken in extension and at 90° of flexion, both before and after implantation of the Triathlon TS Total Knee System.

Intraoperative gap measurements will also be obtained by using lamina spreaders to measure the tibio-femoral distance of the medial and lateral compartments in full extension and at 90° of flexion immediately upon removal of the primary implant and adequate debridement of fibrous tissue down to viable bone. Once the lamina spreaders have been applied within each compartment, a ruler should be utilized against the bone to record the distance between the tibia and femur, in millimeters, if the distance cannot be read directly from the instrument.

If available for intraoperative gap measurements, investigators should utilize a femoral tibial tensor spreader which additionally allows applied force to be read so that consistency is maintained in both extension and flexion. This type of instrument may allow for proper tensing of the medial and lateral ligaments and femoral component rotation, to achieve flexion-extension gap balance.

There are numerous measurements required intraoperatively. Appendix A should be referenced for a full summary on required intraoperative measurements. The majority of intraoperative data required is not standard. Appendix A should be referenced in detail so that all source documentation is reflective of non-standard data points collected. All surgical details needed for data collection can be found in Appendix F, on the Surgical Details Case Report Form (CRF).

2.2 Safety

All operative site events as well as all serious adverse events (SAEs), excluding elective procedures, will be collected and reviewed against published data. It is expected that the AE rates reported for the Triathlon TS Total Knee System will be comparable to those reported in

the literature for similar revision TKR systems. Details regarding AE definitions, recording and reporting are in Section 8 of this protocol, Adverse Events.

3 Clinical Study Plan

3.1 Study Design

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

3.2 Number of Centers

Under Version 1.0 of the protocol, cases were enrolled at 12 centers in the United States. These centers will continue to enroll under Version 2.0. The enrollment goal ranges from 15 to 26 revision TKR cases implanted with the Triathlon TS Total Knee System per center. The enrollment goal range is dependent upon the number of participating centers. Although a range is presented, there is no maximum limit to the number of cases that a center may enroll. In the event that a center far exceeds the enrollment goal, 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 IRB approval. Non-compliance of a study center may result in termination of the center's participation in the study.

3.3 Number of Subjects

Cases will be enrolled in this study until 181 receive the Triathlon TS Total Knee System as required under this protocol. All cases will receive, at a minimum:

- Triathlon TS Femoral Component in a cemented application
- Triathlon TS Plus Tibial Insert or the Triathlon Posteriorly Stabilized (PS) Tibial Insert
- Triathlon TS Universal Tibial Baseplate in a cemented application.

The subject's patellar component may or may not be revised, based upon surgeon discretion. If revised, a Triathlon Patellar Component must be used, and in a cemented application. Additionally, a variety of device accessories may be used. All components are described in detail in Section 6 of this protocol, Device Description.

3.4 Estimated Study Duration

The enrollment period is estimated to be 53 months; cases will be evaluated as per the evaluation schedule until each case reaches 5 years. To allow for a learning curve with the use of the system, enrollment of cases into the study will commence when 3 cases have been completed at the center using the Triathlon TS Total Knee System.

4 Eligibility

The following criteria will be used to distinguish patients eligible for enrollment into this study.

4.1 Inclusion Criteria

A. Patient has signed an IRB approved, study specific Informed Patient Consent Form.
B. Patient is a male or non-pregnant female age 18 years or older at time of study device implantation.
C. Patient is a candidate for revision of all femoral and tibial components of a total knee replacement.
D. Patient is willing and able to comply with postoperative scheduled clinical and radiographic evaluations and rehabilitation.

4.2 Exclusion Criteria

E. Patient has a Body Mass Index (BMI) > 40.
F. Patient has an active or suspected latent infection in or about the affected knee joint at time of study device implantation.
G. Patient has a neuromuscular or neurosensory deficiency, which limits the ability to evaluate the safety and efficacy of the device.
H. Patient is diagnosed with a systemic disease (e.g. Lupus Erythematosus) or a metabolic disorder (e.g. Paget's Disease) leading to progressive bone deterioration.
I. Patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements (e.g. > 30 days).
J. Patient has a failed unicondylar knee prosthesis.
K. Patient has a known sensitivity to device materials.

L. Patient is a prisoner.

Exclusion Criterion F states that an infection cannot exist at the time of study surgery. It should be noted that revision for infection is not excluded. It is expected, however, that for septic failures the infection will be cleared prior to implantation of the Triathlon TS Total Knee System. For example, two-stage exchange may be performed in combination with intravenous antibiotics to clear the infection prior to implantation.[16] Regardless of the method used, Exclusion Criterion F indicates that the infection must be cleared prior to implantation of the Triathlon TS study components.

5 Subject Enrollment

5.1 Treatment Assignment

All subjects enrolled in this study will be assigned to receive the Triathlon TS Total Knee System.

5.2 Randomization

This study will enroll under a non-randomized study design.

6 Device Description

6.1 Study Device

The Triathlon TS Total Knee System has been cleared for marketing in the United States, and, therefore, this study is considered a post-market assessment. All cases in this study will receive, at a minimum, the Triathlon TS Femoral Component, either the Triathlon TS Plus Tibial Insert or the Triathlon PS Tibial Insert, and the Triathlon TS Universal Tibial Baseplate.

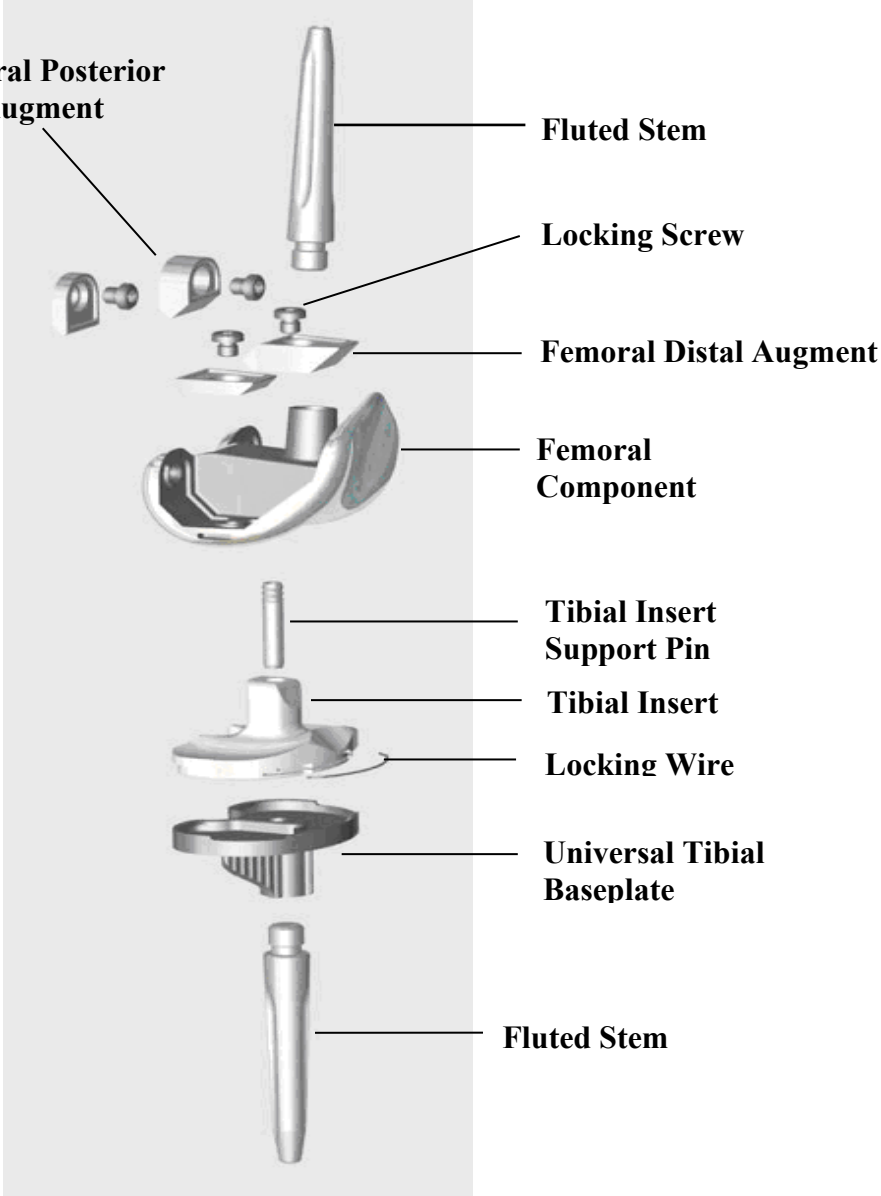
The Triathlon TS Femoral Component and the Triathlon TS Universal Tibial Baseplate must be used in a cemented application. The subject's patellar component may or may not be revised, based upon surgeon discretion. If revised, a Triathlon Patellar Component must be used, and in a cemented application. Additionally, a variety of device accessories may be used.

Device Description:

The Triathlon TS Total Knee System includes femoral components, distal and posterior femoral augments, fluted stems, cemented stems, stem extenders and offset adapters. When mated with the Triathlon TS Universal Tibial Baseplate, tibial inserts and tibial augments, the parts provide a total stabilizing knee replacement.

Figure 1 demonstrates the Triathlon TS Total Knee System excluding the Triathlon tibial augments, cemented stems, stem extenders and offset adapters. Appendix C lists all components permissible according to this study protocol.

Figure 1. Triathlon TS Total Knee System



FEMORAL COMPONENTS

The Triathlon TS Femoral Component is intended for use in a cemented application. The root catalog number for the Triathlon TS Femoral Component is:

5512-F-XXX –Triathlon TS Femoral Component

The femoral component is available in right and left configurations, and eight proportional sizes (1 – 8) to accommodate differences in patient anatomy. The femoral component is manufactured from cobalt chrome. This component features an intercondylar box that engages the mating tibial insert eminence at approximately 40°, depending upon the size of the implant. The interior surface (except for the interior surface of the TS box) is grit-blasted to increase the surface roughness. This is intended to promote interdigitation of the polymethylmethacrylate (PMMA) bone cement with the surface texture and apposing bone. The superior portion of the box has a boss to allow for modular stem and offset attachments. There are threaded attachment features on the distal and posterior aspects of the femoral component to be used for distal and posterior augments. The threaded attachment on the distal aspect of the component also allows for the use of modular pegs.

TIBIAL TRAY:

The Triathlon TS Total Knee System is compatible with the Triathlon TS Universal Tibial Baseplate, which is intended for use in a cemented application. The root catalog number for the Triathlon TS Universal Tibial Baseplate is:

5521-B-XXX – Triathlon TS Universal Tibial Baseplate

The Triathlon TS Universal Tibial Baseplate, or tibial tray, is available in sizes 1 – 8, is fabricated from cast cobalt-chromium-molybdenum alloy and is neutral in configuration. The undersurface of the tibial tray and keel are grit blasted for interdigitation with PMMA bone cement. The keel of the tibial tray is designed with normalizations for rotational stability and cement interdigitation. The superior aspect of the tibial tray has a rim that contains tabs that mate with the outer periphery of the tibial insert, along with the locking wire used on the tibial insert. This locking feature is designed to provide secure attachment of the tibial insert to the tray, and is designed to reduce micromotion of the tibial insert on the tray.

TIBIAL INSERTS

A total stabilizing tibial insert has been developed for use with the Triathlon TS Total Knee System, in sequentially cross-linked UHMWPE (X3) and N2Vac. The Triathlon TS Plus Tibial Insert is available in sizes 1 – 8, with thicknesses ranging from 9 mm to 31 mm. Each insert size is provided in nine thicknesses to vary the resection gap.

The tibial insert design is intended to provide ± 2° of varus/valgus constraint when mated with the Triathlon TS Femoral Components.

The Triathlon TS Plus Tibial Insert features a preassembled cobalt chrome locking wire that secures the tibial insert in the groove of the Triathlon TS Universal Tibial Baseplate. The Triathlon TS Plus Tibial Insert also features a support post that accommodates a cobalt chrome tibial support pin, assembled intraoperatively. The tibial insert support pin is intended to provide additional strength and structural integrity of the knee construct compared to other systems without a support post.

The Triathlon PS Tibial Insert is also compatible with the Triathlon TS Total Knee System and may be used in this study. The root catalog numbers for the tibial inserts permissible according to this study protocol are:

5537-G-XXX – Triathlon TS Plus Tibial Insert
5532-G-XXX – Triathlon PS Tibial Insert, X3
5532-P-XXX – Triathlon PS Tibial Insert, N2Vac

X3 polyethylene is a highly cross-linked polyethylene manufactured through a proprietary process where the polyethylene receives 30 kiloGrays of gamma radiation, which generates free radicals and cross-linking in UHMWPE prior to machining. The polyethylene is then annealed below melting point to promote cross-linking and maintains mechanical strength[a], crystallinity[b] and density[c]. This also stabilizes the free radicals[d]. This process is repeated twice.

[a] X3 UHMWPE maintains mechanical properties for Tensile Yield Strength and Ultimate Tensile Strength of N_2Vac gamma sterilized UHMWPE as measured by ASTM D638. Tensile Yield Strength was 23.2 ± 0.4 MPa and 23.5 ± 0.3 MPa for N_2Vac UHMWPE and X3 UHMWPE, respectively. Ultimate Tensile Strength was 54.8 ± 2.5 MPa and 56.7 ± 2.1 MPa for N_2Vac UHMWPE and X3 UHMWPE, respectively.

[b] X3 UHMWPE has similar crystalline and lamellar structure as N_2Vac gamma sterilized UHMWPE as measured by Small Angle X-ray Scattering (SAXS) and Differential Scanning Calorimetry (DSC) analysis. DSC determined crystallinity was 61.3 ± 0.8% and 61.7 ± 0.6% for N_2Vac UHMWPE and X3 UHMWPE, respectively. Lamellar crystal thickness was 23.0 and 23.6 nanometers for N_2Vac UHMWPE and X3 UHMWPE, respectively.

[c] X3 UHMWPE increases cross-link density over N_2Vac gamma sterilized UHMWPE by 87%, as measured by swell ratio, per ASTM F2214. Cross-link density, as measured by swell ratio, was 0.08 ± 0.00 mol/dl and 0.15 ± 0.01 mol/dl for N_2Vac UHMWPE and X3 UHMWPE, respectively.

PATELLAR COMPONENTS:

Triathlon Patellar Components for use with the Triathlon TS Total Knee System are available in symmetric and asymmetric styles. The components are intended for use in a cemented application for the purposes of this study protocol. The cementless (metal-backed) option in the asymmetric patellar component design is not permissible.

The root catalog numbers for the Triathlon Patellar Components are:

5550-G-XXX – Triathlon Patellar Component, Symmetric, X3
5550-L-XXX – Triathlon Patellar Component, Symmetric, N2Vac
5551-G-XXX – Triathlon Patellar Component, Asymmetric, X3
5551-L-XXX – Triathlon Patellar Component, Asymmetric, N2Vac

The symmetric design is available in six diameters (27 mm, 29 mm, 31 mm, 33 mm, 36 mm and 39 mm) and four thicknesses (8 mm, 9 mm, 10 mm and 11 mm). The symmetric design features a central cement recess and three pegs on the bone interface surface. The Triathlon Symmetric Patellar Component is intended to be implanted via a resurfacing or inset surgical technique. The asymmetric design is available in five superior/inferior dimensions (29 mm, 32 mm, 35 mm, 38 mm and 40 mm) and three thicknesses (9 mm, 10 mm and 11 mm). The asymmetric design features a flare in the lateral aspect of the component. The asymmetric patellar component also has a central recess with three pegs for cement fixation. The Triathlon Asymmetric Patellar Component is intended to be implanted using a resurfacing surgical technique.

ACCESSORIES:

Stems

Fluted stems, manufactured from titanium alloy, are offered in diameters of 10-25 mm (in 1 mm increments) and lengths of 100 mm and 150 mm. The fluted stems are designed to attach to both the femoral and tibial components of the Triathlon TS Total Knee System. One end of the

[d] X3 UHMWPE virtually eliminates free radicals, as measured by Electron Spin Resonance (ESR). A very low (noise level, near instrument detection limit) concentration of residual free radicals was detected in the X3 UHMWPE. A 99% reduction of free radicals ($14 \pm 2 \times 10^{14}$ spins/gram versus $1550 \pm 32 \times 10^{14}$ spins/gram) was found when compared to N_2Vac gamma sterilized UHMWPE.

fluted stems is threaded and locks into the threaded boss of the femoral and tibial components. The stems are tapered and have a 16 mm diameter at the base, which corresponds to the boss diameter of the Triathlon TS Universal Tibial Baseplate and the Triathlon TS Femoral Component. The stems are intended for use when additional length and stability are required in the tibia or femur. The fluted stems are intended to be implanted without the use of bone cement. The root catalog numbers for the Triathlon Fluted Stems are:

5565-S-XXX – Triathlon Fluted Stem, 100 mm
5566-S-XXX – Triathlon Fluted Stem, 150 mm

In the event a cemented stem is needed, the components are offered in diameters of 9 mm, 12 mm and 15 mm, with lengths of 50 mm, 100 mm or 150 mm.

The root catalog number for the Triathlon Cemented Stem is:

5560-S-XXX – Triathlon Cemented Stem

Stem Extenders and Offset Adapters

Stem extenders and offset adapters will be available for use with the Triathlon TS Total Knee System. The Triathlon Stem Extenders provide additional stem length options for the system (25 mm and 50 mm), while the Triathlon TS Offset Adapters allow for varying stem placement within the femoral and tibial canals.

Each component is manufactured from cobalt chrome and is designed to attach to the Triathlon TS Femoral Component, Triathlon TS Universal Baseplate and stems. Additionally, the stem extenders can be attached to the offset adapters. The Triathlon Stem Extenders and Triathlon TS Offset Adapters have the male thread of the stems and the female thread of the tibial tray and femoral component stem bosses.

The root catalog numbers for the stem extenders and offset adapters permissible for use according to this study protocol are:

5571-S-XXX – Triathlon Stem Extender
5570-S-XXX – Triathlon TS Offset Adapter

Femoral Augments

For cases with severely inadequate medial or lateral femoral bone stock requiring additional fixation of the femoral components, femoral augments are included in this system. Posterior and distal femoral augment components are available for attachment to the Triathlon TS Femoral Component with a locking screw. The Triathlon TS Femoral Components feature a threaded hole that accepts the locking screws.

The femoral distal augments are made from cobalt chrome and are grit-blasted. The augments are offered in sizes 1 – 8 and are available in 5 mm, 10 mm and 15 mm thicknesses with right and left options. The posterior femoral augments are also made from cobalt chrome and are grit-blasted. The posterior augments are provided in sizes 1 – 8 with 5 mm and 10 mm thicknesses. The femoral augments have a threaded hole that accommodates a cobalt chrome locking screw, packaged with the augment. The Triathlon Femoral Augments can be cemented to the Triathlon TS Femoral Component.

The root catalog numbers for the femoral augments and accompanying locking screw permissible according to this study protocol are:

5540-A-XXX – Triathlon Femoral Distal Augment, 5 mm
5541-A-XXX – Triathlon Femoral Distal Augment, 10 mm
5542-A-XXX – Triathlon Femoral Distal Augment, 15 mm

5543-A-XXX – Triathlon Femoral Posterior Augment, 5 mm
5544-A-XXX – Triathlon Femoral Posterior Augment, 10 mm

5540-A-000 – Triathlon Femoral Augment Locking Screw
5545-A-000 – Triathlon Femoral Augment Locking Screw

Tibial Augments

Medial and lateral tibial augment components are available in right and left configurations for mechanical attachment to the Triathlon TS Universal Tibial Baseplate. The tibial augments are attached to the baseplate and a pre-assembled setscrew is then rotated to engage with a slot machined into the outer edge of the baseplate keel. This allows the tibial augment to lock

securely onto the baseplate. The tibial augments are made from cobalt chrome and are offered in sizes 1 – 8, in 5 and 10 mm thicknesses.

The root catalog numbers for the tibial augments permissible according to this study protocol are:

5545-A-XXX – Triathlon Tibial Half Block, 5 mm Augment
5546-A-XXX – Triathlon Tibial Half Block, 10 mm Augment

6.2 Device Retrieval Process

Stryker Orthopaedics will retrieve any Triathlon TS Total Knee System components and/or adjacent tissues for analysis to help characterize potential device-related complications. In the event that any portion of the Triathlon TS Total Knee System is removed from a study subject, the procedure outlined in the Retrieval Analysis Protocol (Appendix I) should be followed. In addition:

1. When revision of a study subject is scheduled, the study coordinator (SC) should contact the Clinical Study Manager (CSM) or Clinical Study Associate (CSA) assigned to the project, as soon as possible.
2. The CSM or CSA 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 I.
4. The SC, an identified field representative or the CSM/CSA will complete a Product Experience Report (PER).
5. If not completed by the CSM or CSA, the PER should be faxed to Stryker Product Surveillance at 201-831-6775, as well as to Stryker Clinical Research at 201-831-6454.
6. The PER should be attached to the retrieval container and sent to Product Surveillance. A de-identified operative report should be included, when available.
7. The CSM or CSA will follow up with Product Surveillance to obtain a PER number.
8. A summary of results will be provided to the investigator upon his/her request.

7 Evaluations

7.1 Preoperative Visit

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 approved study consent form prior to participating in any study related activities. Consent must be obtained within four months of surgery.

Once the subject has been consented, preoperative data will be collected including: demographics, medical history, KSS, AP, ML and Merchant (30° of flexion) radiographs, SF-36, KOOS, HSS Patella Score, and LEAS. All information collected preoperatively will be used to quantify the sample population and compare postoperative progress.

7.2 Surgery

Surgical details will be collected from the operative notes and at the time of surgery. Additional information, other than standard operative notes, includes the following measurements: study-specific surgical times; navigation data, if applicable; flexion-extension gap measurements and component fit. Measurements, in millimeters, of the thickness of the flexion and extension space between the ME and the JL will also be collected.

7.3 6-week Visit

During the 6-week visit (± 2 weeks), the following evaluations will be collected: KSS, AP, ML and Merchant (30° of flexion) radiographs.

7.4 6-month Interval

During the 6-month interval (± 2 weeks), completion of the following evaluations is required: SF-36, KOOS, HSS Patella Score and LEAS.

7.5 Annual Follow-up Visits

Clinical data will be collected via office visit by the investigator at the following annual postoperative intervals: 1-year, 2-year and 5-year. Tools for postoperative evaluation will be the KSS, AP, ML and Merchant (30° of flexion) radiographs.

Patient outcomes data will also be collected via patient questionnaires. At each of the 1-year, 2-year and 5-year follow-up visits, the SF-36, KOOS, HSS Patella Score and LEAS are required. Patient questionnaires may be given to subjects in the office during intervals that require clinical data collection.

8 Adverse Events

8.1 Reporting of Adverse Events

The AE reporting requirements for this study are as follows:

- All AEs that meet the definition of serious, excluding elective procedures
- All AEs related to the operative site, regardless of seriousness

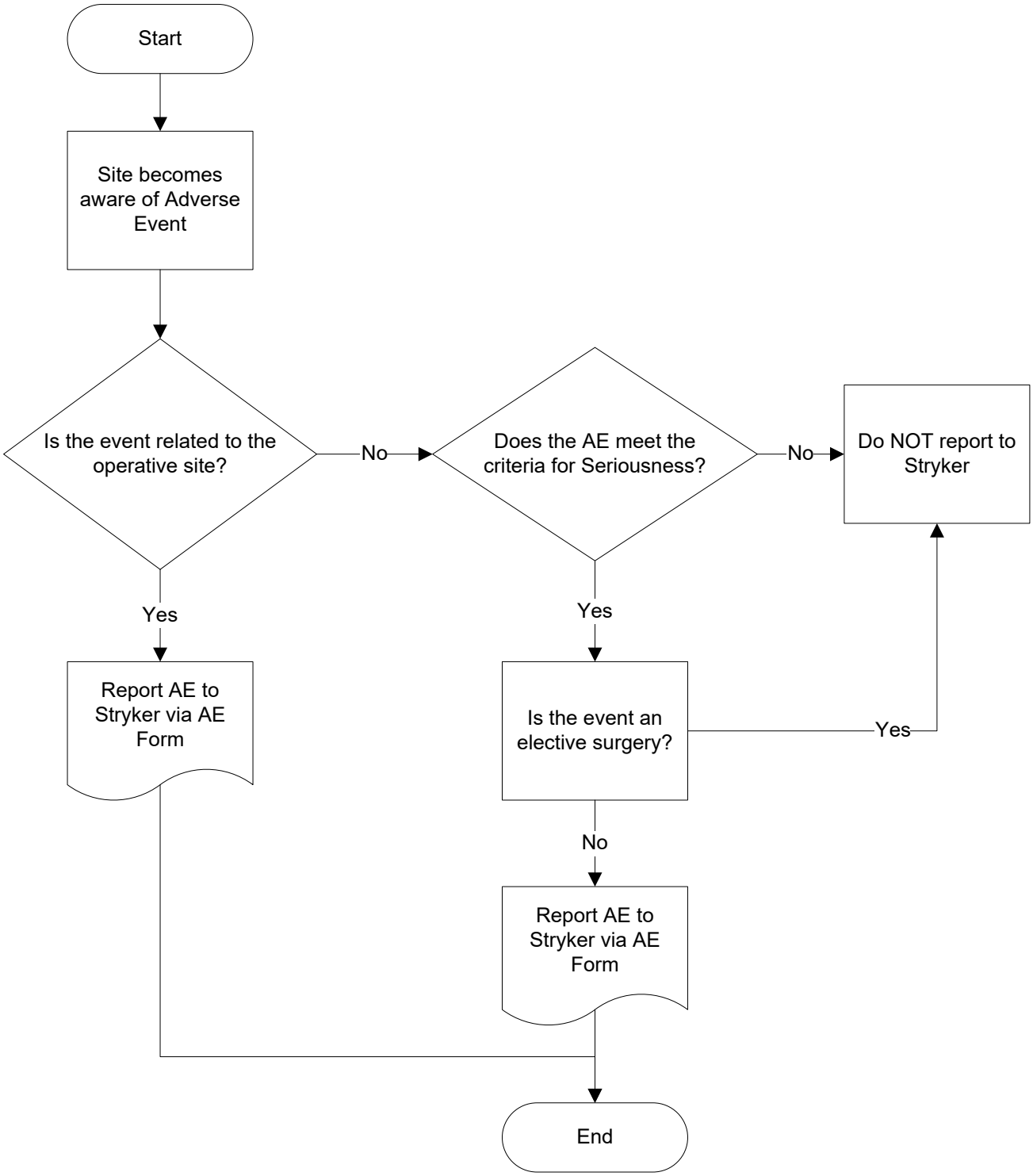
Elective procedures meeting the definition of an SAE do not need to be reported as AEs according to this study protocol. Examples of such elective procedures include, but **are not limited to**, the following commonly seen events:

- Contralateral TKR
- Total Hip Replacement
- Rotator Cuff Surgery
- Cataract Surgery

Such events will not be captured on the AE CRF but rather will be captured on the postoperative functional evaluation at the 6-week, 1-year, 2-year and 5-year time points. On these 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.

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

Figure 2. 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 CRF. 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 CRF. 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.

8.2 General Adverse Event Definitions

Following is a list of general AE definitions. For the purposes of this study, only SAEs, 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 8.1, 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 study protocol. The list of anticipated events is provided in Section 12, Risk/Benefit Assessment.

Serious Adverse Event

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

- Resulted in in-patient hospitalization
- Resulted in prolonged existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Resulted in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
- Was a life-threatening situation
- Resulted in patient death

Elective procedures meeting the definition of a SAE do not need to be reported as AEs according to this study protocol.

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.

8.3 Study Sponsor Fax 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 the study sponsor (CSM or CSA) either by telephone/fax/email <u>within 24 hours of the site's becoming aware of the event if any of the following apply</u>:

- 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.

An AE CRF must be completed by the investigator and submitted to Stryker within 24 hours. The investigator will keep a copy of this AE CRF on file at the study center and submit the hard copy as per CRF data submission procedures. If a SAE occurs, the de-identified source documentation must be submitted within 24 hours of the investigative center's SAE awareness. These reports will be evaluated by Stryker to determine if a Product Experience Report (PER) is required. Report SAEs to:

Michael Howard
Phone: 201-831-5807
Fax: 201-831-6807
michael.howard@stryker.com

Danielle Anthony
Phone: 201-831-5498
Fax: 201-831-6498
danielle.anthony@stryker.com

It is recommended that all other reportable adverse events are reported on eCRFs and submitted to Stryker within 2 weeks.

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

8.3.1 Ethics Committee/Institutional Review Board Notification by Investigator

Reports of AEs (including follow-up information) must be submitted to the Ethics Committee (EC) or Institutional Review Board (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.

8.4 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.

8.5 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 noted above. Stryker will conduct formal investigations via the Product Surveillance Department of those AEs which are submitted through our PER System.

9 Statistical Plan

9.1 Efficacy

9.1.1 Primary Efficacy Parameters

The primary efficacy parameters will be total KSS, KSS pain score and KSS functional score, recorded at 2 years postoperative.

9.1.2 Secondary Efficacy Parameters

The secondary efficacy parameters will include:

- KSS pain and function score changes from preoperative at 1, 2 and 5-year visits
- SF-36 changes from preoperative at 1, 2 and 5-year visits
- KOOS changes from preoperative at 1, 2 and 5-year visits
- HSS Patella Score changes from preoperative at 1, 2 and 5-year visits
- LEAS score changes from preoperative at 1, 2 and 5-year visits

9.1.3 Primary Efficacy Hypothesis

For the primary efficacy hypothesis, H_0, the total KSS change from preoperative to 2 years postoperative will be less than or equal to δ. The alternative hypothesis, H_{1a}, will be that the total KSS change from preoperative to 2 years postoperative is greater than δ. When δ=63 (see explanation in Section 9.4.2, Sample Size Calculation), the hypothesis will test for non-inferiority. When δ=70, the hypothesis will test for superiority.

H_0: $\mu_{2\text{-year}} - \mu_{preop} \leq \delta$

H_a: $\mu_{2\text{-year}} - \mu_{preop} > \delta$

9.1.4 Primary Efficacy Analysis

A one-sided 95% confidence interval of the total KSS change from preoperative to 2 years postoperative (2 years - preoperative) will be computed at 2 years postoperative. For the non-inferiority comparison, the lower bound of this confidence interval will be compared with 63. For the superiority comparison, the lower bound of this confidence interval will be compared with 70.

9.1.5 Secondary Efficacy Analysis

A two-sided 0.05 alpha level will be used.

For the secondary efficacy parameters when data is available, comparisons of numerical variables between subgroups (e.g. JL groups) will be made by a paired t-test or Wilcoxon rank sum test; comparisons of categorical variables between subgroups will be made by a Fisher's exact test.

One-way analysis of covariance (ANCOVA) may be used as a supportive analysis to determine if the score change from preoperative is significantly different between the subgroups after adjusting the preoperative covariates (e.g. age, gender, BMI), if appropriate.

The mean score improvement from the preoperative time point within the Triathlon® TS Outcomes Study will be summarized in tables at each nominal visit. A p-value will be presented to determine if the mean score improvement from the preoperative time point is non-zero, if appropriate.

9.2 Safety Parameters

9.2.1 Safety Parameters

Safety parameters will include all AEs reported, radiographic stability at 1, 2 and 5-year visits and revision rates.

9.2.2 Safety Analysis

All AEs will be listed, tabulated and summarized by event, number and percent of cases/subjects. AE rates and 95% confidence intervals will be presented. In addition, a Fisher's exact test will be used to compare the AE rates between the subgroups or cohorts, if appropriate.

For categorical variables, such as radiographic stability, revision rates and complications, the number and percent in each category will be presented.

9.3 Missing Data

No missing data will be imputed for the primary analysis and secondary analyses.

9.4 Statistical Methodology

9.4.1 Data Summary

The following is a detailed proposal of statistical analyses planned for data collected during the study.

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

Descriptive statistics and statistical comparisons for important demographic, efficacy and safety variables will be provided in tables.

Statistical analyses will use SAS® software version 9.1 or higher.

9.4.2 Sample Size Calculation

A total of 181 cases implanted with the Triathlon TS Total Knee System will be enrolled in the study. The mean total KSS improvement expected, as compared from preoperative to 2 years postoperative, is 70 points.[17] It is assumed that the mean total KSS improvement from preoperative to 2 years postoperative for cases implanted with the Triathlon TS Total Knee System will be comparable to the expected rates (not 10% or 7 points worse), above 63 points. Given a standard deviation of 35 for the improvement in scores, 80% power, and a one-sided 0.05 alpha level to test the 10% (7 points) non-inferiority hypothesis, a sample size of 154 subjects will be required to meet the primary efficacy objective. By factoring in a 15% lost to follow-up rate within 2 years, a total enrollment of 181 subjects will be needed.

9.4.3 Interim Analyses and Early Stopping Considerations

No interim analysis is planned.

9.4.4 Efficacy Patient Populations

9.4.4.1 Efficacy

Per Protocol Population: The study population for analysis will include all subjects who receive the Triathlon TS Total Knee System. This does not include cases censored from analysis for a reason that may have a significant impact on outcome.

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

9.4.4.2 Safety

Safety Population: The study population for analysis will include all subjects who receive the Triathlon TS Total Knee System. This does not include cases censored from analysis for a reason that may have a significant impact on outcome.

9.4.4.3 Survival Analysis

Modified intent to treat population: Subjects enrolled in the study who received the Triathlon TS Total Knee System will be included in the survival analysis.

9.4.4.4 Censored Cases

In the event that a protocol deviation occurs which could affect subject outcome, the data for the affected subject will be censored from the Efficacy and Safety Subject Populations. All cases that fall into this category will be reported separately.

10 Study Procedures

10.1 Subject Recruitment and Screening

Patients will be recruited at the study centers during preoperative visits through normal referral patterns. All patients recruited for this study will have the capacity to give informed consent. Advertising for the study at each center will be at the discretion of the investigator. See Appendix D for samples of study advertisements. All handouts, brochures, advertisements, etc. must be approved by the IRB prior to the dissemination of any recruitment materials to potential subjects.

10.2 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 E 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 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 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.

10.3 Early Withdrawal of Subjects

When and How to Withdraw Subjects

In the event that a subject is discontinued by the investigative center prior to the final study evaluation, the subject will be notified by the center that they are no longer in the study and a Study Termination CRF 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 CRF 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:

- Triathlon TS Femoral Component
- Triathlon TS Universal Tibial Baseplate
- Triathlon TS Plus Tibial Insert or
  Triathlon PS Tibial Insert

Revision or removal of a femoral component or tibial baseplate constitutes a failure and study termination for the subject.

If tibial insert exchange is required during the study, the event is considered a reoperation and does not constitute a failure or study termination.

Patellar component revision at the time of study surgery is optional. However, if the subject requires patellar component revision a Triathlon Patellar Component must be used.

If the patellar component is not revised at the time of study surgery and is later revised, it must be revised to a Triathlon Patellar Component. This event is considered a reoperation and does not constitute a failure or study termination.

If a Triathlon Patellar Component is implanted at the time of study surgery and is revised again during the course of the study, the event is considered a reoperation and does not constitute a failure or study termination. A Triathlon Patellar Component must be used.

Use of ancillary devices at the time of study surgery is optional. However, if the patient requires ancillary devices, the protocol-specified components must be used.

If ancillary devices are not used at the time of study surgery and are needed at a later date during the course of the study, protocol-specified components must be used. This event is considered a reoperation and does not constitute a failure or study termination.

If any protocol-specified ancillary devices implanted are revised or removed at a later date, this would constitute a removal but would not result in failure or termination.

If the subject fails to return for their 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 CRF 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. If the surgery is rescheduled more than 4 months from the date of preoperative data collection, the subject will need to be re-consented, all preoperative data will need to be re-collected and all original preoperative data will need to be removed from the database. If the surgery is not to be rescheduled or if the subject is no longer considered an appropriate study candidate, a Study Termination CRF may be completed **only after notifying Stryker of the subject's status** and **being given approval to terminate**.

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

11 Data Management

11.1 Database

Data will be collected at each center and sent to Stryker for entry into a database which will reside at Stryker. Subject data will be collected, processed and monitored according to the protocol schedule by Stryker or Stryker representatives. Final CRFs are provided in Appendix F.

11.2 Confidentiality

This study will comply with the 2002 privacy rule of the Health Insurance Portability and Accountability Act (HIPAA). 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 will not be 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 withdrawal of authorization in order to maintain data integrity.

11.3 Source Documents

Source data is all information, original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinic 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 follow-up visits must be documented in the subject's chart. This includes ROM values, pain and function, AEs and additional comments. The informed consent process should also be documented in the patient chart. Monitors, defined further in Section 13, will be comparing the CRFs against source documents for adequacy. The monitors will seek to draw a reference between each data point on the CRF 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.

11.4 Case Report Forms

The study CRFs are the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D." If the item is not applicable to the individual case, write "N/A." All entries should be printed legibly in blue or black ink. If any entry error has been made, to correct such an error draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **Do not erase or white out errors**. For clarification of illegible or uncertain entries, print the clarification above the item, initial and date it.

For specific instructions on CRF completion, please consult the Guide to Case Report Forms provided under separate cover. It is recommended that CRFs be completed, signed by the investigator and returned to Stryker within 2 weeks of the evaluation date.

11.5 Data Clarification Forms

If errors or omissions are noted by Stryker upon receipt of the forms, a data clarification form (DCF) will be sent to the center. DCFs should be answered in a clear and comprehensible manner. If the DCF requires a change to data captured on a CRF, the CRF should be modified accordingly. The DCF should clearly document changes independent of the CRF to which it refers. DCFs must be signed and dated by the investigator. It is recommended that completed DCFs be returned to Stryker within 2 weeks of receipt. Modified CRFs need not be included in conjunction to answered DCFs.

11.6 Protocol Deviations

Any deviation from this protocol will be reported to or identified by Stryker and will be reported to the EC/IRB according to their required reporting procedures. Protocol Deviations for this study include, but are not limited to, the following:

- 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
- Unavailable primary endpoint

11.7 Records Retention

It is the investigator's responsibility to retain study essential documents for 2 years after the date of the final report, or in the case of non-compliance, 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.

12 Risk/Benefit Assessment

12.1 *Risk Category*

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

12.2 Potential Risk

The study involves the routine assessment of a revision TKR. The device under study has been cleared for marketing by the FDA and will be used according to its labeling. Assessment involves questionnaires, patient and physician assessments and routine radiographs. The information collected will be kept confidential and will comply with the HIPAA.

Adverse effects associated with revision TKR include the following:

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 and 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 or UHMWPE. Particulate is generated by interaction between components as well as adhesion, abrasion and fatigue. Secondarily, particulates can also be generated by third body wear. Osteolysis can lead to future complications, including loosening, necessitating the removal and replacement of prosthetic components.

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

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

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.

Metal sensitivity reactions have been reported following joint replacement.

AEs may necessitate reoperation, revision, arthrodesis of the involved joint or amputation of the limb.

12.3 *Expected Complications and Rates of Occurrences*

Complications associated with revision TKA procedures, such as those performed with the Triathlon TS Total Knee System, have been reported. These include the potential for: injury to the knee's neurovascular structures, loosening of the components, heterotopic bone formation, infection, deep vein thrombosis, pulmonary embolism, metal sensitivity reactions, intraoperative or postoperative fracture of the femur or tibia, and the need for reoperation, revision, arthrodesis

of the involved joint or amputation of the limb. The safety objective will compare the Triathlon TS Total Knee System complication rates to published rates.

12.4 *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 well being of the subject, this deviation will be promptly reported to both the EC/IRB and Stryker.

12.5 *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 system/device by comparing this treatment/device to published results for other treatments/devices. Information gathered in this study may benefit others undergoing this procedure in the future.

Subjects will have incentives to return for follow-up visits through a retention program. Subjects will earn points for completing each follow-up visit within the windows outlined in the protocol and without protocol deviations. They will then have the opportunity to redeem their points for a gift (See Appendix G, Patient Retention Program). Use of this retention program by centers is optional.

The monetary value of the gifts to the subjects is modest and should not unduly coerce them to participate in the study.

13 Study Monitoring, Auditing, and Inspecting

13.1 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.

This study will be monitored at least once a year, with additional visits 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 and has adequate space to conduct the monitoring visit. The monitor will review all source documents and compare them to the data contained in the CRFs, in addition to performing a periodic review of regulatory documents such as EC/IRB approvals. The monitors will need the following when they visit:

- An area where they can review study data
- Subject case books
- Patient charts pulled at the center
- Regulatory documents
- Time to meet with the SC and the investigator

13.2 Auditing and Inspecting

A quality assurance audit is a form of review that provides additional confidence to a sponsor concerning the validity and accuracy of clinical study data that must 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 a 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.

14 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.

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 should provide a list of EC/IRB members and their affiliates to Stryker, if available.

All patients considered for this study will be provided a consent form describing this study and providing sufficient information for patients to make an informed decision about their participation. See Appendix E for a copy of the Model Informed Patient Consent. This 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 IRB approved consent form, must be obtained before that patient is submitted to any study procedure. This consent form must be signed by the patient or legally acceptable surrogate and the investigator-designated research professional obtaining the consent.

15 Study Finances

15.1 Funding Source

This study is financed by Stryker Orthopaedics.

15.2 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.

15.3 Subject Stipends or Payments

Subjects will have incentives to return for follow-up visits through an optional patient retention program. Subjects will earn points for completing each follow-up visit within the windows outlined in the protocol and without protocol deviations. They will then have the opportunity to redeem their points for a gift (See Appendix G, Patient Retention Program). Use of this retention program by centers is optional.

The monetary value of the gifts to the subjects is modest and should not unduly coerce them to participate in the study.

Subject attrition can occur for a variety of reasons, including a subject's loss of health insurance coverage. In a case where a subject 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. an 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

Under extreme circumstances, and with prior approval, Stryker may reimburse a subject for the cost of transportation to and from the investigator's office for a protocol-required office visit.

This policy is the same for all participating study subjects and does not bias against any particular subject or study cohort.

16 Publication Plan

It is anticipated that publications of the multi-center study results will be compiled and submitted to a peer-reviewed journal at the time the study cohort reaches 2 and 5 years of follow-up. Additional publication proposals may 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.

Publications will be facilitated by the Chair and the primary investigator (PI) of the study, as applicable. Both individuals will be chosen by Stryker.

The PI is solely focused on the multi-center publications and progress towards those publications, including recurring updates to centers, center motivation as well as authorship. If the PI does not produce a draft of a publication within 90 days of receiving the results data, Stryker will delegate the responsibility to other investigators in the study at its discretion.

The Chair reviews all additional publications proposed by participating investigators based upon the study results prior to study completion, on an ongoing basis. This review includes whether or not a proposal will be pursued, as well as imposition of guidelines as to publication completion and criteria. The following summarizes the roles of these parallel positions:

Chair	PI
Contributes to study design	Contributes to study design
Assists with study questions requiring expert clinical opinion	Assists with study questions requiring expert clinical opinion
Assists with identification of investigators	Assists with identification of investigators and maintains performance
Reviews additional publication proposals submitted by investigators	Updates investigators on progress towards multi-center results
Contributing author, if ICMJE guidelines met	Primary author, multi-center publication of primary endpoint data

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 5-year multi-center publication is submitted. 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 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.

17 References

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