CLINICAL PROTOCOL

TITLE: **Scorpio NRG® prospective, open-label, post-market international multicentre outcome Study**

Protocol #: K-S-002 (previous protocol #: SLCRG-001-2007)

NCT#: NCT02524730

Version Date: 2nd Amendment version 1.3 2019JAN09

Sponsor: Stryker Orthopaedics
325 Corporate Drive
Mahwah, NJ 07430
USA

Local Sponsor Representative: Stryker European Operations B.V.
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Confidentiality Statement

Protocol Change History

Version	Description	Reason	Changed by
1.2	Add EQ-5D	Introduced as a standard quality of life evaluation tool	Britta von den Brincken
1.2	Add Exclusion criterion #17 Severe deformities: varus/valgus deformity >10° (mech. axis), bowed femur >20°, flexion contracture >10°	Requested by Chief investigator	
1.3	Change protocol number from SLCRG-001-2007) to K-S-002	Align with general nomenclature of European Clinical Investigations	Britta von den Brincken
1.3	Change Sponsor Responsible	Study is now conducted by Stryker Orthopaedics Mahwah USA; local representative is European Operations B.V.	
1.3	Delete Chief investigator's agreement from signature page	Now covered by the contract	
1.3	Replace ISO14155 Part1 and Part 2 by ISO14155-GCP	All Clinical procedures have been updated to ISO14155-GCP	
1.3	Remove x-ray analysis from objectives	x-rays will not be analysed	
1.3	Update section 1.3 Clinical data to date	Interim report December 2014 available	
1.3	Terminate study after a minimum of 5 years follow-up for each case (already completed 7 years patient follow-up will be included in the analysis)	Significant changes in the company's business as per section 13 of this procedure	
1.3	Update responsible roles and contact details	Changes in study management and procedures	
1.3	Replaced detailed reporting time lines to EC/IRB by "as requested by the responsible Ethic Commission"	Different requirements by ECs/IRBs as notified in approval letter.	

1.3	In section 11 “Personal data protection/Confidentiality” The term “anonymized” was replaced by “pseudonymized”	Align with General data protection regulation	
	Delete Appendices - Patient Information Sheet and Informed Consent Form - Sample Case Report Form - Guide to completing CRFs - Tables of chemical composition	Documents available in Trial master file and Investigation site files	

Table of Contents

STUDY SUMMARY

Title	**Scorpio NRG® prospective, open-label, post-market international multicentre outcome Study**
Protocol Number	K-S-002 (previous protocol number SLCRG-001-2007)
Phase	Post-marketing
Sponsor	Stryker Orthopaedics Mahwah, USA
Study design	Prospective, open-label, international
Study Duration	12 months enrolment period + up to a minimum of 5 years follow-up for each case = ~ 6 years total duration.
Study Centre(s)	5
Objectives	To collect basic function and patient satisfaction data for observation and analysis. Specific objectives include the following: Evaluate the effect of component design on functional performance by comparing postoperative Knee Society Scores with preoperative. Evaluate the effect of component design on patient activity by comparing postoperative Lower Extremity Activity Scale (LEAS) with preoperative. Evaluate patient satisfaction using SF-36® Health Survey. Evaluate quality of life using Knee Injury and Osteoathritis Outcome Score (KOOS) and EuroQol 5D (EQ-5D).
Primary endpoint	Survival (revision rate)
Indication	Primary total knee replacement
Study device / control device	Scorpio NRG® Total Knee System
Number of Subjects	250 Patients (Competitive recruitment)

Inclusion and Exclusion Criteria	Inclusions: 1) Patient is able to understand the meaning of the study and is willing to sign the EC approved, study specific Informed Patient Consent Form. 2) The subject is a male or non-pregnant female between 40 and 75 years of age. 3) The subject requires a primary total knee replacement. 4) Patients with osteoarthritis or posttraumatic arthritis (no rheumatoid arthritis) 5) The subject has intact collateral ligaments. 6) The subject is willing and able to comply with postoperative scheduled clinical and radiographic evaluations and rehabilitation. 7) The subject is capable of understanding the patient scores in the national language. Exclusions: 1) The subject is morbidly obese, defined as Body Mass Index (BMI) of > 40. 2) The subject has a history of total or unicompartmental reconstruction of the affected joint. 3) The subject will be operated bilaterally. 4) Patients who had a Total Hip Arthroplasty (THA) on contralateral and/or ipsilateral side within the last year that is considered to have an unsatisfactory outcome (Patients with contralateral and/or ipsilateral THA > 1 year ago with good outcome can be included in the study). 5) Patients who had a Total Knee Arthroplasty (TKA) on contralateral side within the last year that is considered to have an unsatisfactory outcome. (Patients with contralateral TKA > 1 year ago with good outcome can be included in the study). 6) Patients who will need lower limb joint replacement for another joint within one year. 7) The subject has had a high tibial osteotomy or femoral osteotomy. 8) The subject has a neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device. 9) The subject has a systemic or metabolic disorder leading to progressive bone deterioration. 10) The subject is immunologically suppressed or receiving steroids in excess of normal physiological requirements. 11) The subject's bone stock in compromised by disease or infection which cannot provide adequate support and/or fixation to the prosthesis. 12) The subject has had a knee fusion to the affected joint. 13) The subject has an active or suspected latent infection in or about the knee joint. 14) Proven or suspected hypersensitivity to one or more than one of the device materials. 15) Female patients planning a pregnancy during the course of the study. 16) The subject is a prisoner. 17) Severe deformities: varus/valgus deformity >10° (mech. axis), bowed femur >20°, flexion contracture >10°

Patient evaluations will be performed according to the schedule below:

Table 1 – Evaluation schedule

Evaluation	Pre-OP	Intra-OP	Prior to dis-charge	3 months (± 3 weeks)	1 year (± 2 months)	3 years (± 2 months)	5 years (± 3 months)	7 years** (± 3 months)
Demographics	x							
Medical history	x							
Clinical evaluation	x		x	x	x	x	x	x
Surgical details		x						
KSS	x			x	x	x	x	x
Lower Extremity Activity Scale	x			x	x	x	x	x
KOOS	x				x		x	x
SF-36	x			x	x	x	x	x
EQ-5D	x			x	x	x	x	x
*Radiographs: ap, lateral	x		x		x		x**	x
*Radiograph: merchant view	x			x				
*Radiograph: long leg	x			x				

*Radiographs will not go into analysis

**optional

CLINICAL PROTOCOL PLAN SIGNATURE PAGE

TITLE: **Scorpio NRG® prospective, open-label, post-market international multicentre outcome Study.**

Protocol #: K-S-002

Version Date: 2nd Amendment, Version 1.3 2019JAN09

Prepared by: B.v. d. Brincken 2019FEB18 Britta von den Brincken Clinical Study Manager Stryker Orthopaedics - Joint Replacement Clinical Operations	I confirm correctness of my signature from 2019FEB18
Approved by: Danielle Campbell 19FEB2019 Danielle Campbell Manager, Clinical Research Stryker Orthopaedics - Joint Replacement Clinical Operations	I confirm correct ness of my signature from2019Feb19
19FEB2019 Ellen Axelson Sr. Director Clinical Operations Stryker Orthopaedics - Joint Replacement Clinical Operations	I confirm correctness of my signature from 2019FEB19

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1. Preliminary Investigations and Justification of the Study

This document is a protocol for a clinical investigation. This clinical investigation will be conducted in compliance with this protocol, ISO 14155-GCP, and the applicable regulatory requirements.

1.1. Background

This document is a protocol for a clinical outcome study. This study will be conducted in compliance with the protocol, Good Clinical Practice Guidelines, associated regulations and all applicable research requirements.

Today total knee joint replacements are routinely implanted with total knee arthroplasty being one of the most successful joint reconstructions. The number of total knee replacements is rising worldwide, and patients are increasingly younger at the time of implantation. The developments of the implant design, as well as the improvement of instruments, over the last decades enable sound and reliable results. With increasing success of joint replacement and decreasing age of patients, the expectations of total knee arthroplasty are constantly on the rise. Patients anticipate reduced painkiller, long lifetime of the implant with high functionality and a great range of motion to carry out daily activities and sports. Apart from regaining a lifestyle without major knee pain, some cultural and religious aspects (e.g. kneeing while praying) where deep flexion is required, are a challenge for modern knee-systems.

The Scorpio NRG® Knee System has been designed with these activities in mind. Scorpio NRG® has a greater internal and external rotational freedom throughout the full range of motion when compared to other modern knee replacement designs. Traditional insert designs utilize a less functional partial rotary arc, thus limiting the overall kinematic function of the knee. The Scorpio NRG® tibial insert's articulating surface uses a Spherical Arc motion in order to realize greater freedom. By combining a single M/L radius and a Spherical Arc, Scorpio NRG® allows for greater rotational freedom without restricting the tibio-femoral contact area. Freedom of rotation is one of the most essential factors in the design of a successful total knee replacement, thus allowing the patient's ligaments to govern motion of the knee.

Furthermore, the component design can contribute to patient's activity level by providing joint stability and improved function. While traditional knee implants are designed with several axes of rotation that may create mid-flexion instability during the transition between radii, a single axis and single radius design can provide consistent collateral ligament isometry and stability throughout the range of motion.

In this outcome study of the Scorpio NRG® knee system, we expect improvement of a patient's lifestyle and activities. This study evaluates patients for five (optional seven) years post-surgery. The focus of this study is to evaluate the effect of component design on functional performance and the patient's satisfaction. Thus, the Knee Society Score and the SF-36 is used. Further measures being used include the comparative postoperative with preoperative Lower Extremity Activity Scale (LEAS), Knee Injury and Osteoarthritis Outcome Score (KOOS) and EuroQol 5D (EQ-5D) to evaluate the quality of life.

1.2. Device Description

The Scorpio NRG® Knee System has been CE marked in Europe. This evaluation is therefore considered a post marketing assessment.

In this clinical study, all patients will have the femoral, tibial tray and optional patellar components implanted with bone cement. The Scorpio NRG® Femoral component will be available in Cruciate Retaining (CR) style combined with Scorpio NRG® CR Tibial insert, respectively. In all cases the Scorpio NRG® femoral and tibia inserts will be used in combination with the Tibia Baseplate from the Scorpio® Knee System. A patella component from the Scorpio® Knee System is optional. The components are described below.

FEMORAL COMPONENT:

The Scorpio NRG® femoral components are manufactured from cobalt chromium alloy (ASTM F75) and are available in left and right configurations. The interior surface of the components contains a waffle pattern for the cement interface. These components have been designed to mimic the normal femoral condylar geometry. These components employ a single medial lateral radius, which corresponds with the bearing surface of the intended articulating tibial counterpart. This helps to maintain contact between the femoral condyles and the tibial insert surface throughout the range of motion. The femoral components are available in 9 proportional sizes 3, 4, 5, 6, 7, 8, 9, 11 and 13 (see product brochure).

The Scorpio NRG® CR: Intended for use in combination with the Scorpio NRG® cruciate retaining tibial inserts and the Scorpio® Total Knee System patella components.

TIBIAL INSERT:

The tibial insert components are available in CR and PS designs. Both designs are manufactured from ultra-high molecular weight polyethylene (ASTM F648). Highly crosslinked (X3) polyethylene inserts are to be used in all study patients. A proprietary rotary machining process used on the articulating surface of the tibial insert provides for improved rotation of components. In keeping with the design theory, the tibial insert component employs a single medial-lateral radius. The surface incorporates a posteriorly sloping raised tibial eminence. The insert is assembled to the tibial tray component intraoperatively via a locking wire mechanism. The locking wire is manufactured from wrought cobalt chromium alloy (ASTM F90). The inserts are available in five sizes (3, 5, 7, 9, 11). Each size is available in seven thicknesses 8mm, 10mm, 12mm, 15mm, 18mm, 21mm and 24mm.

TIBIAL BASEPLATE:

The cemented Scorpio® Primary Knee System Tibial Baseplate is to be used in all study cases. The baseplate is manufactured from cobalt-chromium alloy. The Scorpio® Primary Tibial Baseplate is neutral in configuration, and is available in eight proportional sizes (3, 4, 5, 6, 7, 9, 11, 13). The undersurface of the tibial tray has a waffle structure and is designed for use with PMMA bone cement. The keel of the tibial tray is designed with normalizations for rotational stability and cement interdigitation.

PATELLAR COMPONENT:

The use of a patellar component is optional. The Scorpio® System Patellar component is manufactured from highly crosslinked (X3) polyethylene and is available with a superior/inferior medialized offset of 1,5mm.

- medialized dome patella
- concentric dome patella
- universal dome patella

INSTRUMENTATION:

No new instruments have been designed for use with the Scorpio NRG® System. These components will use the currently existing Scorpio® Total Knee System instrumentation. The only exception is the development of the femoral and tibial insert trials that have the same geometry as the implants.

1.3. Clinical Data to Date

As of the interim analysis completed in December 2014, 220 patients were included across 5 centres between May 2009 and December 2013. The mean age, height and weight were 65.3 years, 171.4 cm and 87.9 kg, respectively. All patients received a Scorpio NRG Total Knee System.

The mean assessment and functional components of the Knee Society Score were 57.6 and 61.7 pre-operatively compared to 83.6 and 88.7 at the 1-year follow-up, respectively. Patient scores including the LEAS, KOOS, SF-36 and EQ5D showed an increase between the pre-operative visit and 1-year follow-up visit. There were three prosthesis revisions reported during the first year of follow-up and three patients have decided to withdraw from the trial. This analysis was carried out in the early stages of follow-up, so it is not possible to draw any conclusions about the performance of the prosthesis in this report.

Overall, the patient group showed improved clinical results in early follow-up.

2. Objectives of the Clinical Investigation

The objective of this study is to collect basic function and patient satisfaction data for observation and analysis.

Specific objectives include the following:

- Evaluate the effect of component design on functional performance by comparing postoperative Knee Society Scores with preoperative.
- Evaluate the effect of component design on patient activity by comparing postoperative Lower Lower Extremity Activity Scale (LEAS) with preoperative.
- Evaluate patient satisfaction using SF-36® Health Survey.
- Evaluate quality of life using Knee Injury and Osteoarthritis Outcome Score (KOOS) and EuroQol 5D (EQ-5D).

3. Design of the Clinical Investigation

3.1. Study Design

A prospective, open-label design will be employed. The study is international and multicentre.

3.2. Number of Centers

Cases will be enrolled in up to 5 centres in Europe. See also **Appendix 1** Investigator Contact List.

3.3. Number of Subjects

A total of 250 patients will be enrolled in the study. A competitive recruitment system will be used, meaning patients will be enrolled in all sites until the 250 patients have been recruited.

Enrollment into the study will be stopped when the planned number of patients has been reached between all the study sites (a competitive recruitment system). In the ideal case, this is 50 patients per centre; however, there is no minimum and no maximum number of study patients per site.

3.4. Estimated Study Duration

The enrolment period is estimated to be 12 months. Cases will be evaluated as per the evaluation schedule (Table 1) with follow-up up to a minimum of five years, giving total study duration of approximately six years minimum.

Subjects will be evaluated preoperatively and at follow-up intervals of three months, six months, one year, three years, five years and an optional seven years.

4. Eligibility

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

4.1. Inclusion Criteria

Subjects meeting all the following criteria will be eligible to be enrolled in the study:

1. Patient is able to understand the meaning of the study and is willing to sign the EC approved, study specific Informed Patient Consent Form.
2. The subject is a male or non-pregnant female between 40 and 75 years of age.
3. The subject requires a primary total knee replacement.
4. Patients with osteoarthritis or posttraumatic arthritis (no rheumatoid arthritis)
5. The subject has intact collateral ligaments.
6. The subject is willing and able to comply with postoperative scheduled clinical and radiographic evaluations and rehabilitation.
7. The subject is capable of understanding the patient scores in the national language.

4.2. Exclusion Criteria

Subjects meeting any of the following criteria will not be included in the study:

1. The subject is morbidly obese, defined as Body Mass Index (BMI) of > 40.
2. The subject has a history of total or unicompartmental reconstruction of the affected joint.
3. The subject will be operated bilaterally.
4. Patients who had a Total Hip Arthroplasty (THA) on contralateral and/or ipsilateral side within the last year that is considered to have an unsatisfactory outcome (Patients with

contralateral and/or ipsilateral THA > 1 year ago with good outcome can be included in the study).

5. Patients who had a Total Knee Arthroplasty (TKA) on contralateral side within the last year that is considered to have an unsatisfactory outcome. (Patients with contralateral TKA > 1 year ago with good outcome can be included in the study).
6. Patients who will need lower limb joint replacement for another joint within one year.
7. The subject has had a high tibial osteotomy or femoral osteotomy.
8. The subject has a neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device.
9. The subject has a systemic or metabolic disorder leading to progressive bone deterioration.
10. The subject is immunologically suppressed or receiving steroids in excess of normal physiological requirements.
11. The subject's bone stock in compromised by disease or infection which cannot provide adequate support and/or fixation to the prosthesis.
12. The subject has had a knee fusion to the affected joint.
13. The subject has an active or suspected latent infection in or about the knee joint.
14. Proven or suspected hypersensitivity to one or more than one of the device materials.
15. Female patients planning a pregnancy during the course of the study.
16. The subject is a prisoner.
17. Severe deformities: varus/valgus deformity >10° (mech. axis), bowed femur >20°, flexion contracture >10°

4.3. Discontinuation and Withdrawal of Subjects

The subject's participation in this investigation is voluntary, and the subject has the right to refuse further participation or withdraw from this investigation at any time and without providing a reason.

In the event that a subject is discontinued from the study for any reason, the site will complete a Study Termination form. Subjects may be withdrawn for the following reasons:

- Serious Adverse Event
- Patient Withdrawal
- Revision/Removal of study device
- Lost to Follow-Up
- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's wellbeing.
- At the specific request of the Sponsor
- Completion of study and final evaluation

If the patient fails to return for their follow-up appointments, every effort should be made to contact the subject to assess their health status. If after attempting to contact the patient

through three documented phone calls. If the patient still does not respond, the patient will be considered as “lost to follow-up”. A Study Termination Form will be completed after notifying Stryker of the patient’s status.

In the event that the subject is discontinued by the investigative site prior to the final study evaluation, the subject is notified that they are no longer in the study and a Study Termination form will be completed.

Following discontinuation, the subject will be seen regularly as considered clinically appropriate. If the discontinuation was caused by an adverse event the subject will be seen regularly until the symptoms have disappeared or are under control, or until feasible treatment has been undertaken. Refusal to participate or early withdrawal from this investigation will not affect the quality or availability of the subject’s medical care.

Subjects withdrawn from the study will keep their subject number. New subjects must always be assigned a new subject number. In the event that the subject withdraws from this investigation, the information that has already been collected will be included in the database and in the final analyses. The subject’s medical records will also be available for monitoring, auditing and inspection purposes.

5. Subject Enrolment

5.1. Subject Recruitment and Screening

Patients will be recruited at the study sites during preoperative visits through normal referral practice. All patients recruited for this study will have the capacity to give their informed consent on the ethics committee approved, study specific Informed Patient Consent Form.

5.2. Patient Informed Consent and Guidelines

The subject will be informed by the Investigator (or his designated representative) of the purpose of the study, study duration, and follow-up schedule. All foreseeable risks and potential benefits, which might occur during and after total knee arthroplasty, will be discussed with the subject.

The subject will be informed that his/her medical records are subject to review by representatives of the sponsor as necessary. The confidentiality of the subject will be maintained at all times. The subject will be told that he/she is free to refuse study participation or to withdraw from the study at any time without compromising future medical care.

All subjects for this study will be provided with a consent form describing this study giving sufficient information for subjects to make an informed decision about their participation in the study.
The informed consent must contain all elements required by local and institutional policies. The document must be translated into the local language(s) applicable in each study site, be understandable to the subject and must specify who informed the subject. When required by local regulations, the person informing the subject must be a physician. This consent form will be submitted with the protocol for review and approval by the IEC/IRB for the study.

All subjects must provide written consent of their willingness to participate in the study after having had adequate time to consider their decision. The formal consent of a subject, using the EC-approved consent form, must be obtained before that subject is submitted to any protocol related procedures that are not part of the subject’s normal care. Written documentation of

consent must be provided on the consent's signature page in addition to a note in the patient medical records indicating the date that consent was obtained. The investigator obtaining the consent must also sign this consent form. The subject or their legal representative should receive a signed copy of the consent.

All patients receive information about the limitation of the study duration to five, optional 7 years.

5.3. Treatment Assignment

All subjects enrolled in this study are assigned to receive the Scorpio NRG Total Knee System.

5.4. Randomization Procedures and Unblinding

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

5.5. Supplies/Device Accountability

The study devices must be stored and handled in accordance with the manufacturer's guidelines. The Investigator will also keep accurate records of the devices assigned to each subject.

The investigator will be asked to attach the labels (with the lot device number), where possible, of the implanted devices to the corresponding patient CRF page in order to keep a tracking of the devices.

6. Evaluations

Subjects will be evaluated preoperatively and at follow-up intervals of three months, one year, three years, five years and an optional seven years (see Tables 1 and 2). Each subject will be followed for a minimum of five years post-implantation. All subject evaluations will be documented by completion of appropriate Case Report Forms.

Table 2 – Evaluation schedule (functional and patient assessment)

Evaluation	Pre-OP	Intra-OP	Prior to dis-charge	3 months (± 3 weeks)	1 year (± 2 months)	3 years (± 2 months)	5 years (± 3 months)	7 years** (± 3 months)
Demographics	x							
Medical history	x							
Clinical evaluation	x		x	x	x	x	x	x
Surgical details		x						
KSS	x			x	x	x	x	x
Lower Extremity Activity Scale	x			x	x	x	x	x
KOOS	x				x		x	x
SF-36	x			x	x	x	x	x
EQ-5D	x			x	x	x	x	x
*Radiographs: ap, lateral	x		x		x		x**	x
*Radiograph: merchant view	x			x				
*Radiograph: long leg	x			x				

*Radiographs will not go into analysis

**optional

Basic demographic and medical history information are to be collected at the most two months prior to surgery. This information includes age and gender. Height, weight, primary diagnosis, concurrent medical condition and prior treatment to the affected joint are also documented at this time.

6.1. Surgical Procedure

Standard, accepted surgical procedures for total knee arthroplasty will be utilized. The specific surgical procedure performed at each investigative site is to be documented before study start. All study patients are to be operated on according to the relevant site-specific surgical procedure. Any deviations from this site-specific surgical procedure are to be documented.

After surgery, information is to be collected concerning the surgical details and hospital course of the subject. Information such as length of surgery (skin to skin, tourniquet, instrumentation, and anesthetic times); surgical approach; soft tissue released; ASA Classification; range of motion at discharge; intraoperative complications and prosthesis implanted is recorded.

Appropriate postoperative care will be given and is at the discretion of the physician, as is weight bearing schedule.

Rehabilitation time frame and regimen performed at each investigative site is to be documented before study start. All study patients are to be rehabilitated according to the relevant site-specific rehabilitation procedure. Any significant deviations from this site-specific rehabilitation procedure are to be documented.

6.2. Functional Evaluation

All subjects participating in the study are to be evaluated functionally utilizing the KSS, LEAS, KOOS, and EQ-5D preoperatively and at each protocol specified follow-up interval (see Table 2). Clinical assessment is based on an evaluation of pain and function.

Specific parameters include:

- Pain intensity
- Range of motion
- Stability
- Anatomic alignment
- Walking/standing ability
- Stair climbing ability
- Use of walking aids

To allow for accurate measurement of the range of motion a goniometer should be used. It is of particular importance that a sterile goniometer is used during the surgery to measure the intraoperative range of motion.

6.3. Patient Assessment Evaluations

Data will be obtained from the subjects with the use of standard health status questionnaires. The SF-36 is designed to measure overall evaluation of health, functional status and wellbeing from the subject's perspective. The LEAS is designed to measure patient activity. The patient's quality of life will be measured by the KOOS and EQ-5D. Subjects will be asked to complete the questionnaires preoperatively and at each follow-up evaluation interval specified in the protocol (see Table 2).

7. Adverse Events

7.1. Definitions

Adverse Event (AE) – "Any untoward medical occurrence in a subject whether it is considered to be device related or not. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease developed or worsened during the period of observation in the study, whether or not related to the investigational product"

An Adverse Event could be:

- a new illness
- worsening of an illness
- an effect of the study device including the comparator (if any)
- a combination of two or more of these factors

Surgical procedures themselves are not Adverse Events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event if it occurs or is detected during the study period. Planned surgery measures permitted by the study and the condition(s) leading to these measures are not adverse events. If the condition(s) was (were) known before the subject enrolled in the study, this (these) should be recorded in the medical history CRF.

Adverse Device Effect (ADE) – "Any untoward or unintended response to a medical device including any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device and any event that is a result of user error"

Serious Adverse Event (SAE) – An adverse event that:

- Led to a death, or
- Led to serious deterioration in the health of the subject that:
  – resulted in a life-threatening illness or injury.
  – resulted in a permanent impairment of a body structure or a body function.
  – required in-patient hospitalization or prolongation of existing hospitalization.
  – resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function, or
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

The term "life threatening" in the definition refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Serious Adverse Device Effect (SADE) – "adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune"

7.2. Recording of Adverse Events

Once the subject has signed the informed consent, information on all adverse events should be recorded immediately in the source document.

Any adverse event which occurs during the reporting period which is related to the device or meets the definition of serious should be documented via a Serious Adverse Event Form. AE's can be documented via an Adverse Event Form. All complications will be treated with appropriate medical care.

Any device-related Adverse Event will be documented in detail as indicated on the CRF. The following information is required:

- Onset date of the AE
- Description of the event (All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the source document, though they should be grouped under one diagnosis on the CRF)
- Seriousness of the event
- Intensity of the event (mild, moderate or severe; see definitions below)
- Relationship of the AE to the investigational device (see definitions below)
- Any action taken to resolve the AE
- Outcome of the AE (recovered, recovered with sequela, or on going)
- Stop date of the AE if not indicated as on going

7.2.1. Intensity

The investigator is to classify the intensity of an AE according to the following definitions:

Mild: Transient symptoms, no interference with the subject's daily activities.

Moderate: Marked symptoms, moderate interference with the subject's daily activities.

Severe: The subject is unable to perform usual activity.

7.2.2. Relationship

The investigator is to classify the investigational device relationship of an AE according to the following definitions:

Not related: The time between implantation of the investigational device and occurrence or worsening of the AE rules out a causal relationship, and/or another cause is confirmed and no indication of involvement of the investigational device in the occurrence/worsening of the AE exists.

Unlikely: The time between implantation of investigational device and occurrence or worsening of the AE makes a causal relationship unlikely, and/or the known effects of the investigational device provide no indication of involvement in occurrence/worsening of the AE, and another cause adequately explaining the AE is known, and/or regarding the occurrence/worsening of the AE a plausible causal chain may be deduced from the

known effects of the investigational device, but another cause is much more probable, and/or another cause is confirmed and involvement of the investigational device in the occurrence/worsening of the AE is unlikely.

Possibly: An AE that might be due to the use of the device. An alternative explanation (e.g. concomitant drug(s), concomitant disease(s)) is inconclusive. The relationship in time is reasonable; therefore, the casual relationship cannot be excluded.

Probably: An AE that might be due to the use of the device. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely (e.g. concomitant drug(s), concomitant disease(s).

Definitely: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge)

The clinical course of each device-related event should be followed until resolution, stabilisation, or until it has been determined that the study treatment or participation is not the cause.

7.3. Reporting of Serious Adverse Events and Adverse Device Events

7.3.1. Study Sponsor Notification by Investigator

Any serious adverse event or adverse device event must be reported by the Investigator to the Safety Responsible at Stryker by telephone within 24 hours or at the latest on the following working day.

A Serious Adverse Event Form must be completed by the investigator and faxed to Stryker within 3 working days. The reporting language is English. The investigator will keep a copy of this SAE form on file at the study site. Serious Adverse Events should be reported by phone to the Clinical Study Manager and the site specific responsible CRA.

7.3.2. EC Notification by Investigator

Reports of serious adverse events - including follow-up information - must be submitted to the Ethics Committee (EC) as requested by the responsible Ethic Commission. Copies of each report and documentation of EC notification and receipt will be kept in the Investigator Site File and also in the study Master File.

7.4. Period of Observation

For the purpose of the study, the period of observation for collection of adverse events extends from the time the subject gives informed consent until the date of last study visit or last contact with the subject.

7.5. Medical Monitoring

It is the responsibility of the Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

8. Risk Assessment

8.1. Risk Category

There is minimal risk associated with participating in this study over and above that of the primary knee arthroplasty procedure.

8.2. Potential Risk

The study involves the routine assessment of a knee arthroplasty procedure. The device under study has been cleared for marketing and has the CE mark. It will be used according to its labelling. Assessment involves questionnaires, patient and physician assessments, and routine x-rays. The information collected will be kept confidential.

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 ultra-high molecular weight polyethylene (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 and/or 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.

Adverse events may necessitate reoperation, revision and in rare cases arthrodesis of the involved joint, girdle stone or amputation of the limb.

8.3. Protection Against Risks

Patients 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 patient, this deviation will be promptly reported to the Ethics Committee and a protocol deviation form shall be completed.

8.4. Potential benefits to the Subject

In addition to the benefits from the primary knee arthroplasty procedure e.g. reduced pain, improved range of motion, there is no guarantee that patients will personally benefit from inclusion in this study. Patients 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.

9. Statistical Plan

9.1. Statistical Methods

Descriptive statistics will be computed for all baseline conditions and demographic parameters. For parameters represented by continuous variables (e.g., ROM), the summaries will consist of the mean, median, standard deviation, minimum, and maximum values. For categorical variables, the number and percent in each category will be presented. If appropriate, the data will be presented by appropriate subgroups (e.g., centre, gender). Descriptive statistics and statistical comparisons for important demographic, efficacy, and safety variables will be provided in tables.

A survival analysis will be performed to according to the number of revision surgeries.

9.2. Missing Data

No imputation of missing data will be made. If any questionnaire (e.g., KSS) has a missing item, the total score for that scale will be considered missing.

9.3. Protocol Deviations

Any deviation from this protocol will be recorded with an explanation for the deviation and reported to Stryker who is responsible for analysing them and assessing their significance. Protocol deviations will be reported to the IEC/IRB according to the local IEC/IRB's reporting procedures.

Protocol Deviations for this study include the following:

- Informed consent process is not carried out according to ISO 14155
- Subject enrolled does not meet the inclusion/exclusion criteria.
- Subject is not implanted with study device.
- Subject not seen in the specified follow-up window.
- Surgical protocol not followed.

If the site anticipates a possible protocol deviation, the investigator or study coordinator should contact Stryker for guidance. For the examples cited above, it is likely that the patient would be excluded, and a Study Termination form completed.

10. Quality Management

10.1. Study Monitoring Plan

This investigation will be monitored regularly by monitors appointed by Stryker to review the compliance with the clinical investigation plan, ISO 14155 and with applicable regulatory requirements. 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 depending on the recruitment rate. The first monitoring visit is to take place after the recruitment of the first patient and then at least quarterly during the enrolment period and at least twice per year during the follow up periods, 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 the source documents and compare them to the data contained in the case report forms, in addition to performing a periodic review of the Investigator Site File. The monitors will need the following when they visit:

- An area where they can review records
- Patient case report forms
- Signed Patient Informed Consents
- Source documents (Patient charts, radio graphs, etc.)
- Investigator Site File
- Time to meet with the study coordinator and the Investigator

Clinical data reports are considered as containing source data and are therefore regarded as confidential and available for review only by the sponsor's authorised representative, clinical investigators and their ethics committees or by regulatory authorities if required for audits.
The sponsor's clinical monitor will check data accuracy and quality before taking the case report forms and leaving a copy on side. Informed consent and source data relevant to the study are inspected but are not be removed from the side.

10.2. Case Report Forms

Stryker will provide the Case Report Forms (CRF) to the investigators. The investigator should ensure the accuracy, completeness, legibility and timelines of the data reported to Stryker in the CRFs and in all required reports.

Data reported on the CRF, which is derived from source documents, should be consistent with the source documents or any discrepancies should be explained.

All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank as a procedure was not performed or the question was not asked, "N/D" should be inserted. If the item is not applicable to the individual case, "N/A" should be inserted. All entries should be printed legibly in ink. If an error has been made on entering data,

corrections should be made by drawing a single straight line through the incorrect entry and entering the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item and then initial and date it.

Case report forms should be completed as soon as the information is available, signed by the investigator, and be ready for review before the monitor visits the site.

10.3. Data Management

Data will be collected at each site (description of process see paragraph 10.1. study monitoring plan) involved in the study and sent to Data Management at Stryker for entry into a database. Patient data will be collected, processed and monitored according to the protocol schedule by the clinical research group at Stryker. If errors or omissions are identified by Data Management upon receipt, a data clarification form (DCF) will be sent to the site for clarification. Completed DCFs should be returned to Stryker within two weeks of receipt.

10.4. Quality Assurance/Audit

The investigator will permit study-related monitoring, audits and inspections by the IEC/IRB, Stryker and/or government regulatory bodies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). Procedures will be followed in order to comply with ISO 14155 guidelines. The investigator will ensure the capability for inspections of applicable study-related facilities.

11. Ethical Considerations

11.1. International Standards

This study is to be conducted according to globally accepted standards of ISO 14155, in agreement with the “Declaration of Helsinki” and in accordance with local regulations.

11.2. Delegation of Investigator Duties

The investigator should ensure that all persons assisting with the study are adequate qualified, informed about the study procedures, any amendments and their study-related duties and functions.

The investigator should maintain a list of co-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

11.3. Subject Information and Informed Consent

In accordance with the Declaration of Helsinki all centres must gain written Ethics Committee approval prior to enrolling patients in the study. Ethics Committee approval must be gained either from the local responsible Ethics Committee at the investigator site or from an adequately constituted (as according to ISO14155) independent Ethics Committee.

11.4. Patient Insurance

All patients enrolled in this trial are covered by general liability insurance and where required insurance according to national regulations is taken out by Stryker. The name address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator Site File.

11.5. Personal data protection/Confidentiality

Stryker affirms and upholds the principle of the patient rights to protection against invasion of privacy. All data recorded in the CRFs or data used in further evaluations are coded by patient number. In all data analyses the identity of patients will remain pseudonymous. Pseudonymised patient data may be stored and electronically processed by Stryker for the purpose of scientific evaluation and may be forwarded to a company and/or an authority located in and outside Europe for registration purposes. Only authorized representatives of Stryker, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and health authorities will have allowed access to personal medical records for the sole purpose of checking the accuracy of data collected in the trial.

As such, Stryker will only collect information that is necessary to support the objectives of the clinical trial. Stryker will take precautions to ensure that data received is as unidentifiable as possible. If Stryker receives information which would allow the identification of a patient, it will ensure that such information will be deleted and will not be transferred. Study subjects will authorize Stryker to use their health information in support of the clinical trial according to the Informed Consent Process. Should a subject choose to withdraw authorization, Stryker may use data collected prior to the withdrawal of authorization in order to maintain data integrity.

The Investigator will maintain a personal subject identification list (i.e. subject numbers with the corresponding subject names) to enable records to be identified.

All patients remaining in the study receive information regarding data protection according to EU 2016/679 General Data Protection Regulation.

11.6. Legal Approvals

Before the study starts, the Clinical Investigation Plan, Informed Consent Form and any other applicable documents will be submitted to the IEC/IRB with a cover letter or a form listing the documents submitted noting the version dates. If applicable, the documents will also be submitted to the relevant authorities in accordance with local regulatory requirements.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The investigator must keep a record of all communication with the IEC/IRB. This also applies to any communication between the investigator and the authorities.

The investigator shall submit progress reports, annual reports and a final report to the responsible ethics committee, as required by the local IEC/IRB’s reporting procedures.

12. Amendments to the Clinical Investigation Plan

Amendments are changes made to the clinical investigational plan, after approval from the relevant ethics committee.

A 'substantial amendment' is defined as an amendment to the terms of the ethics committee application, or to the protocol or any other supporting documentation that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects in the study,
- the scientific value of the study,
- the conduct or management of the study or
- the quality or safety of any intervention used in the study.

Where necessary, Ethics Committee/Institutional Review Board, competent authorities or the regulatory bodies will be informed.

Non-substantial amendments must not be notified to the accredited ethics committee but are recorded and filed by the sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons stated in the submitted study documentation.

All amendments to the Clinical Investigation Plan will be agreed between Stryker and the clinical investigators. Amendments will be recorded along with a justification for the amendment.

13. Early Termination or Suspension of the Investigation

At the discretion of Stryker, the entire investigation may be cancelled for medical reasons. In addition, Stryker retains the right to end the investigation at any time if the investigation cannot be carried out as agreed in the Clinical Investigation Plan or for reasons of significant changes in the company's business. In case of premature termination, Stryker will promptly inform the investigators/institutions. In addition, the regulatory authorities and IRBs/IECs will be informed according to the local requirements of the termination or suspension and the reason for such termination.

14. Record Retention

Both administrative and patient related documents are kept by the Sponsor for two years after the study termination. Administrative and patient data at the clinical investigational site is kept according to site and local country regulations. The investigator must obtain approval in writing from the Sponsor before destruction of any study records/documentation.

15. Study Financial Arrangements

The local sponsor representative Stryker European Operations B.V. holds contracts with the medical institutions of the investigation sites on behalf of the Sponsor Stryker Orthopaedics Mahwah, USA. The financial aspects of the study will be documented in an agreement between Stryker European Operations B.V. and the investigator/institution.

16. Publication Policy

It is anticipated that a publication of the study results will be compiled and submitted to a peer-reviewed journal. The primary investigator of the multi-centre study will be chosen by Stryker and will have the responsibility of being primary author of such publications.

Each surgeon/investigator shall have publication privileges for their own centre's results at the completion of the study. These manuscripts and abstracts will be delayed until after the multi-centre publication is submitted. All publications of the data shall be submitted to Stryker for review at least 60 days 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.

17. List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AP	Anterior-posterior
ASTM	American Society for Testing and Materials
BMI	Body Mass Index
CE	Communauté Européenne
CR	Cruciate Retaining
CRA	Clinical Research Associate
CRF	Case Report Form
DCF	Data Clarification Form
EC	Ethics Committee
EQ-5D	EuroQol 5D questionnaire
IRB/IEC	Institutional Review Board / Independent Ethics Committee

ISO	International Organization for Standardization
KOOS	Knee Injury and Osteoathritis Outcome Score
KSS	Knee Society Score
LEAS	Lower Extremity Activity Scale
ML	Mediolateral
PI	Primary Investigator
PS	Posterior Stabilizing
ROM	Range of Motion
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SF-36	Short-Form 36
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty

18. References

1. World Medical Association Declaration of Helsinki. Ethical Principles for Medical research involving Human Subjects. 2002

2. Clinical Investigation of Medical Devices for Human Subjects. ISO 14155. June 2000

3. EC Medical devices directive for post-market surveillance of CE market joint replacement implants including guidance to manufacturers on post-market clinical studies (September 2000)

4. EU Medical Devices Directive 93/42/EEC concerning Medical Devices. 14 June 1993

5. Guidelines on Post Market Clinical Follow-Up. MEDDEV 2.12-2. May 2004

6. Guidelines on Medical Devices for Evaluation of Clinical Data: a guide for Manufacturers and Notified Bodies. MEDDEV 2.7.1. April 2003

7. Guidelines on a Medical Devices Vigilance System. MEDDEV 2.12-1 rev 4. April 2001

Appendix 1

Investigator Contact List	
Information deleted for data protection reason.	