CLINICAL INVESTIGATION PLAN

TITLE: **Polyethylene Wear Study on the Triathlon Total Knee Prosthesis**

A Prospective Randomized Single Centre RSA Study

Protocol #: Triatlon X3vsN2Vac

Version Date: Version 0.6: 2010-07-18

Sponsor: Stryker SA, Montreux, Switzerland

NCT: 02525588

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STUDY SUMMARY

Title	**Polyethylene Wear Study on the Triathlon Total Knee Prosthesis_A Comparison of a Highly-crosslinked and a Crosslinked PE in-vivo**
Protocol Number	TriX3_2009
Phase	Post-marketing
Sponsor	Stryker SA, Montreux, Switzerland
Study design	A Prospective Randomized Single Centre RSA Study
Study Duration	12 months enrolment period + up to 5 year follow-up for each case = 6 years total duration.
Study Centre(s)	1
Objectives	The primary objective is the assessment of the *in vivo* wear of the two randomized polyethylene inlay types N2Vac and X3 by means of Roentgen Stereophotogrammetry. The secondary objective is the assessment of prosthetic migration results after two years of the Triathlon CS Peri-Apatite coated tibial component by means of Roentgen Stereophotogrammetry. The third objective will be the prediction of the long-term survival of the Triathlon CS Peri-Apatite coated tibial components based on the two-year migration patterns combined with clinical factors and radiographic aspects. Safety data will be collected
Primary endpoint	In-vivo wear of N2Vac inlay vs. X3 inlay
Indication	Primary total knee replacement
Study device / control device	Triathlon CS total knee system
Number of Subjects	100 Patients

Inclusion 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. Patients with a pre-operative knee score of < 70. 3. Patients scheduled to undergo primary total knee replacement with any of the following indication. – Painful and disabled knee joint resulting from osteoarthritis. – One or more compartments are involved. 4. Need to obtain pain relief and improve function. 5. Ability and willingness to follow instructions, including control of weight and activity level, and to return for follow-up evaluations. 6. A good nutritional state of the patient. 7. Full skeletal maturity of the patient, patients who are at least 18 years of age. 8. Patients of either sex.

Exclusion Criteria	Exclusions: 1. The subject is morbidly obese, defined as Body Mass Index (BMI) of > 40. 2. Skeletal immaturity of the patient, patients who are less than 18 years of age. 3. Patient has a flexion contracture of 15° and more. 4. Patient has a varus/valgus contracture of 15° and more. 5. Patients with a pre-operative knee score of >70. 6. The subject has a history of total or unicompartmental reconstruction of the affected joint. 7. The subject will be operated bilaterally. 8. 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). 9. Patients who had a Total Knee Arthroplasty (TKA) on contralateral side within the last 6 months that is considered to have an unsatisfactory outcome. (Patients with contralateral TKA > 6 months ago with good outcome can be included in the study). 10. The subject has an active or suspected latent infection in or about the knee joint 11. Osteomyelitis 12. Sepsis 13. Patients who will need lower limb joint replacement for another joint within one year. 14. The subject has a neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device. 15. The subject has a systemic or metabolic disorder leading to progressive bone deterioration. 16. The subject is immunologically suppressed or receiving steroids in excess of normal physiological requirements. 17. The subject's bone stock in compromised by disease or infection which cannot provide adequate support and/or fixation to the prosthesis. 18. The subject has had a knee fusion to the affected joint. 19. Female patients planning a pregnancy during the course of the study. 20. The patient is unable or unwilling to sign the Informed Consent specific to this study

Patient evaluations will be performed according to the schedule below:

Table 1 – Evaluation schedule

	Pre -op	Op	< 1wk (prior to discharge)	6wk	3m	6m	1yr	2yr	5 yr
Range (weeks)				±4d	±1wk	±2wks	±4wks	±4wks	±6ks
Demographic Information	✓								
Historical Record	✓								
Clinical Evaluation			✓	✓	✓	✓	✓	✓	✓
Operative Record		✓							
Knee Society Score	✓			✓	✓	✓	✓	✓	✓
SF-36	✓			✓	✓	✓	✓	✓	✓
EQ 5-D	✓			✓	✓	✓	✓	✓	✓
Lower-Extremities Activity	✓			✓	✓	✓	✓	✓	✓
RSA analysis			✓	✓	✓	✓	✓ **(double)**	✓	✓
Radiographic imaging	✓ **AP/ Lat**		✓ **Lat**	✓	✓ **Lat**	✓	✓ **Lat**	✓ **Lat**	✓ **Lat**
Adverse Events (including revision)		**Anytime**							

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

TITLE: **Polyethylene Wear Study on the Triathlon Total Knee Prosthesis**

Protocol #: Triathon X3vsN2Vac

Version Date: Version 0.5: 2010-03-10

Prepared by: _____ _____

Eric H. Garling, Ph.D.
Clinical Research Manager
Stryker GmbH & Co.KG, Germany

Approved by: _____

Hanna Schlyter
Director Clinical Research Europe
Stryker SA

I agree:

- To conduct the trial in compliance with ISO 14155 guidelines, with the applicable regulatory requirements, and with the protocol agreed to by the sponsor and given approval/favourable opinion by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

- To comply with procedures for data recording/reporting
- To permit monitoring, auditing and inspection
- To retain the essential documents that should be in the investigator/institution files until the sponsor informs the investigator/institution these documents are not longer needed

Signed by: _____

H. Kaptijn, MD
Department of Orthopaedics
't Langeland Ziekenhuis Zoetermeer

CONTACT INFORMATION

Principal investigator	H. Kaptijn, MD Department of Orthopaedics 't Langeland Ziekenhuis Zoetermeer
Co-investigator	R. de Ridder, MD Department of Orthopaedics 't Langeland Ziekenhuis Zoetermeer
Orthopaedic surgeons	P. Langendijk, MD Department of Orthopaedics 't Langeland Ziekenhuis Zoetermeer V. Rudolphy, MD Department of Orthopaedics 't Langeland Ziekenhuis Zoetermeer
Radiology	J. Kuiper, MD Department of Radiology 't Langeland Ziekenhuis Zoetermeer R. Olsthoorn Department of Radiology 't Langeland Ziekenhuis Zoetermeer
RSA analysis (CRO)	ClinFact, *a Medis specials b.v. company* Hans Reiber, CEO Leiden, The Netherlands
Research Coordinators	A. van Dam Clinical Research Associate Stryker Nederland

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 Part 1 and 2 Guidelines, and the applicable regulatory requirements.

1.1. Introduction

The most common causes for failure after more than 2 years after primary total knee surgery are polyethylene wear and aseptic loosening (Dennis, 2004; Fehring et al., 2001; Sharkey et al., 2002). Cumulative 10 year revision rates of total knee arthroplasty (according to the Swedish Knee register report) have generally decreased over the past 25 years probably due to improvements in implant design, more accurate instrumentation and polyethylene quality. However, there is a general trend towards treating younger patients and these younger and probably more active patients are likely to generate more wear and hence this may contribute to a new increase of wear and revision rates seen in (younger) patients.

The Posterior Stabilized (PS) knee prosthesis is the most implanted total knee prosthesis design in the world. In PS knees articulation of the femoral component is facilitated by the use of a post and cam interaction providing the anterior-posterior sliding necessary to reach optimal (high) flexion. Research indicates that the high degree of tibial-femoral conformity and stability, which characterizes PS knees, plays an important role in the long-term durability and survivorship of 90% after 15 year of this design (Aglietti *et al*., 1999, Stern & Insall, 1992). However, it has also been shown that posterior stabilized implants contribute to additional wear debris. Especially at anterior and posterior locations of the post severe wear has been observed (Puloski et al., 2001).

Ultra high molecular weight polyethylene (UHMWPE) is nowadays the standard material used for the articulating surface. Recently a cross-linking process improved the mechanical properties of polyethylene with double or even triple cross-linking procedures arising. An example of a triple cross-linked polyethylene is X_3 (Stryker, Warsaw, USA). Theoretically and *in vitro* X3-polyethylene has improved wear resistance over conventional and current generation cross-linked polyethylene. It improves wear reduction over conventional polyethylene with 97%; the mechanical properties are maintained so that structural fatigue, yield strength and ultimate tensile strength are equivalent to virgin polyethylene and it resists oxidation. However, so far no clinical *in vivo* data has shown the benefits of this new material for tibial bearings. Combining this new material with a PS design should theoretically lead to superior wear characteristics and consequently long-term durability and survivorship of the prosthesis.

Therefore, it would seem logical to develop an alternative bearing surface in total knee replacements to attempt to reduce wear by applying the newest generation of polyethylene in combination with the successful characteristics of a PS knee. On theoretical ground this knee prosthesis will potentially further improve survivorship and function of these implants. The Triathlon CS insert (Stryker, Warsaw, USA)

substitutes the posterior cruciate function (like normal PS knees) without the use of a post. This will remove the additional wear observed in PS knees without compromising function and stability. The insert is available in a conventional polyethylene (N2Vac) and the newest generation polyethylene (X3).

To test new bearing concepts on a large scale in a general population, using national registries as the primary benchmarking tool, is by definition not a good idea. Firstly, the main endpoint in registers is usually revision and all tribological failures, radiological or clinical, do not have to lead to revision. Secondly, due to the relatively low observed revision rate, the size of the population to be studied has to be large (several thousands) and to be followed over an extended period of time (5-10 years) in order to detect statistically significant differences (Robertsson, 2007). Therefore to study wear and fixation of new implants accurate outcome parameters have to be used.

Roentgen Stereophotogrammetric Analysis (RSA) is a very accurate measurement technique used to obtain micromotion of the implants relative to inserted tantalum markers in the surrounding bone. The accuracy of RSA mentioned in the literature ranges from 0.01 to 0.7 mm for displacement. It has been applied in many studies, mostly in Sweden (Kärrholm, 1989). In 2000, the Orthopaedic Department of the Leiden University Medical Center developed a Model-based RSA system (Model-based RSA, Medis specials BV, Leiden, The Netherlands). The accuracy of this software in clinical studies is about 0.25 mm for translations and 0.2° for rotations in the 95% confidence interval (Hurschler et al., 2006; Kaptein et al., 2003; Vrooman et al, 1998). Kärrholm et al. (1994) and Ryd et al. (1995) showed that with RSA a long-term prediction can be made of prosthetic loosening based on a two years follow-up.

The goal of this study is to compare conventional UHMWPE with X_3 highly cross-linked polyethylene in a CS fixed bearing total knee prosthesis (Triathlon Knee System: Stryker, Warsaw, USA) by means of RSA and clinical evaluation.

1.2. Description of the Devices

The Triathlon® Knee System (Stryker, Warsaw, USA) is designed to help provide patients more natural-like motion, a better anthropometric fit and the potential for greater implant longevity, e.g. in reduction of Polyethylene related wear. The design goal was to optimize rotation in deep flexion while providing stability. The unique design of the Triathlon Knee with its anatomic single-radius replicates proper tracking of the epicondyles, creating natural soft-tissue tension that promotes stability, allows for deep flexion and facilitates the tibial rotation necessary to support deep flexion activities. This will mimic natural knee motion, enhancing stability and mobility during daily activities. These design characteristics offer the potential for enhanced long-term component durability.

Triathlon Peri-Apatite coated Tibial component:

All tibial components are Peri-Apatite coated. The crystals deposited from the Peri-Apatite form a Hydroxy- Apatite coating with an overall average thickness of 20 µm which allows for bone in-growth.

Prostheses are available in eight different (1-8) so the best suited size is used for the patient based on the pre-operative evaluation and planning.

The participating surgeons will use Stryker instruments for prosthesis placement. The instruments will be used conform the instructions of the manufacturer.
(Cat. # 5526-B-X00 Triathlon Primary PA coated)

Triathlon Peri-Apatite coated Femoral component:
All femoral components are Peri-Apatite coated. The crystals deposited from the Peri-Apatite form a Hydoxy- Apatite coating with an overall average thickness of 20 µm which allows for bone in-growth.
Prostheses are available in eight different (1-8) so the best suited size is used for the patient based on the pre-operative evaluation and planning.
The participating surgeons will use Stryker instruments for prosthesis placement. The instruments will be used conform the instructions of the manufacturer.
(Cat. # 5517-F-XXX Triathlon CR PA coated)

Polyethylene insert N2Vac:
Ultra high molecular weight polyethylene (UHMWPE) is a linear polymer with a molecular weight of 4 – 6 Daltons. In solid form the crystallinity is about 50%. The numerous tie molecules connecting the crystalline regions give this polymer high impact and wear resistance. For over 40 years UHMWPE has been used as a bearing surface for total hip or knee joint replacement.
Packaging and sterilisation techniques are important factors affecting for the longevity of this material. The N_2Vac packaging process consists of two steps: Nitrogen packaging and Gamma irradiation to limit the risk of oxidation during irradiation.
(Cat. #: 5531-P-XXX Triathlon CS N_2Vac Insert)

Polyethylene insert X3^{TM}:
X3 polyethylene offers advanced mechanical strength, improved wear reduction and resistance to oxidation by placing the material through a sequentially irradiation and annealing progressive crosslinking process. This patented process preserves the polyethylene´s microstructure for optimal strength and fatique benefits. It makes X3^{TM} suitable for higher stress applications such as knees, so these patients may benefit from the potentially longer wearing properties of a highly crosslinked material.
(Cat. # 5531-G-XXX Triathlon CS X3 Insert)

1.3. Beads

To evaluate the motion of the polyethylene bearing and micromotion of the prosthesis, at least three well-scattered tantalum balls (ø 1.0 mm) have to be inserted into the tibia and femoal bone. To this end a special designed Ta-marker insertion device will be used according to instructions of the manufacturer (Halifax Biomedical, NS, Canada). The beads are not part of the Knee system itself. The bead inserter

device will be loaned to the hospital by Stryker for the duration of the clinical study (covered in study contract).

2. Objectives of the Clinical Investigation

- The primary objective is the assessment of the in vivo wear of the two randomized polyethylene inlay types N2Vac and X3 by means of Roentgen Stereophotogrammetry. It is expected that the X3 group will show significantly less wear after 5 years compared to the conventional N2Vac polyethylene group.

- The secondary objective is the assessment of prosthetic migration results after two years of the Triathlon CS Peri-Apatite coated tibial and femoral components by means of Roentgen Stereophotogrammetry. It is expected that due to the superior wear qualities of X3 polyethylene this group will show significantly less migration of the prosthesis' components after two-years compared to the components in the N2Vac group.

- The third objective will be the prediction of the long-term survival of the Triathlon CS Peri-Apatite coated tibial and femoral components based on the two-year migration patterns combined with clinical factors and radiographic aspects. In order to identify other clinical parameters besides wear influencing the fixation of the prosthesis components, clinical scores and radiographic aspects will be correlated with the RSA outcome. Subsequently, a long-term prediction can be for the Triathlon CS Peri-Apatite coated tibial and femoral components.

3. Design of the Clinical Investigation

3.1. Study Design

Single-Center Randomized Controlled Trial (RCT) to compare conventional UHMWPE with X3 highly cross-linked polyethylene in a CS fixed bearing total knee prosthesis.

All Patient recruitment and RSA image acquisitions will take place in: 't Lange Land Ziekenhuis, Zoetermeer.

The Quality Control of the RSA images and RSA image analysis will be carried out by the CRO (ClinFact, Leiden, the Netherlands).

3.2. Number of Subjects

RSA is able to measure wear with high accuracy. Previous RSA wear studies show that the expected wear rate is 0.13 ± 0.08 mm a year (Short et al., 2005; Kellett et al., 2004). A clinical relevant difference to detect differences in wear would be a standard deviation of 0.1 mm a year.

Group sample sizes of 27 patients in each group would achieve 95% power to detect a difference of -0.1 mm wear between the null hypothesis that both group means are 0 and the alternative hypothesis that the mean of group 2 is 0.1 with estimated group standard deviations of 0.1 and with a significance level (alpha) of 0.05 using a two-sided two-sample t-test.

However, in order to also achieve the third objective of this protocol whereby clinical parameters will be correlated with RSA results, more patients are needed to obtain stronger correlations with the important

clinical outcome parameters. Taking the latter in account and to compensate for possible lost to follow up, 50 patients will be recruited per study group.

3.3. Randomisation

After signing Informed Consent, the patients will be randomised in one of the two groups, the day before surgery. Randomization envelopes will be provided by Stryker to the primary investigator. The patient will receive either the **N_2Vac polyethylene** inlay or the **X3 polyethylene** inlay for their CS total knee. .
The principal investigator and the participating surgeons may dissent from the randomisation scheme based on intra-operative findings. This patient will be excluded from the study.

4. Eligibility

General inclusion/exclusion criteria for patients undergoing primary total knee arthroplasty will be used as guidelines for this study. Subjects selected for this evaluation must meet the following criteria in order to be enrolled in to the study:

4.1. Inclusion Criteria

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

9. Patient is able to understand the meaning of the study and is willing to sign the EC approved, study specific Informed Patient Consent Form.
10. Patients with a pre-operative knee score of < 70.
11. Patients scheduled to undergo primary total knee replacement with any of the following indication.
    - Painful and disabled knee joint resulting from osteoarthritis.
    - One or more compartments are involved.
12. Need to obtain pain relief and improve function.
13. Ability and willingness to follow instructions, including control of weight and activity level, and to return for follow-up evaluations.
14. A good nutritional state of the patient.
15. Full skeletal maturity of the patient, patients who are at least 18 years of age.
16. Patients of either sex.

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. Skeletal immaturity of the patient, patients who are less than 18 years of age.
3. Patient has a flexion contracture of 15° and more.
4. Patient has a varus/valgus contracture of 15° and more.

5. Patients with a pre-operative knee score of >70.
6. The subject has a history of total or unicompartmental reconstruction of the affected joint.
7. The subject will be operated bilaterally.
8. 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).
9. Patients who had a Total Knee Arthroplasty (TKA) on contralateral side within the last 6 months that is considered to have an unsatisfactory outcome. (Patients with contralateral TKA > 6 months ago with good outcome can be included in the study).
10. The subject has an active or suspected latent infection in or about the knee joint
11. Osteomyelitis
12. Sepsis.
13. Patients who will need lower limb joint replacement for another joint within one year.
14. The subject has a neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device.
15. The subject has a systemic or metabolic disorder leading to progressive bone deterioration.
16. The subject is immunologically suppressed or receiving steroids in excess of normal physiological requirements.
17. The subject's bone stock in compromised by disease or infection which cannot provide adequate support and/or fixation to the prosthesis.
18. The subject has had a knee fusion to the affected joint.
19. Female patients planning a pregnancy during the course of the study.
20. The patient is unable or unwilling to sign the Informed Consent specific to this study

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.

4.3.1 Specific Criteria for Withdrawal /Termination

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:

- Patient failure – defined by the requirements at the two- year follow-up interval see section 6.1.3.
- Any Serious Adverse Event that effects the outcome of the study
- Any Serious Adverse Event related to the test device
- Revision/Removal of study device
- Patient withdrawal (patients own request
- Lost to Follow-Up

- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well being (a written explanation is required)
- Completion of study and final evaluation
- Death of the subject

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 3 documented phone calls and a certified (i.e., return-receipt) letter, 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.

After withdrawal subjects will not be replaced to the study.

5. Subject Enrolment

5.1. Subject Recruitment and Screening

Patients will be recruited during preoperative visits through normal referral practice.

If the patient fulfills the study criteria, the surgeon informs the patient concerning the study and gives the information letter. The surgeon will answer remaining questions at the next visit. If the procedure is clear and the patient agrees to participate, the informed consent is signed and the preoperative questionnaires are obtained. 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. If the patient does not want to participate or does not fulfill the inclusion criteria, he/she will obtain the normal clinical follow-up.

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. See Appendix 1 for a copy of the Patient Information Sheet and Informed Consent Form. 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.

5.3. Randomization, Blinding and Treatment Allocation

The patients will be randomized to receive N2Vac polyethylene inlay or the X3 polyethylene inlay (see section 3.3). The randomization will occur via a random number generator (manual or computer). The doctor or other health care professional does not choose the participants for each group. For patients satisfying inclusion criteria, randomisation will occur by retrieving the next randomly generated group assignment. The patient, physiotherapist (for the clinical evaluation) and data analyzers (RSA data, clinical data, radiographic data and statistics) will be blinded. The PI and other participating surgeons have no influence on the collection of the (clinical) data and the data analysis.

5.4. The Operative Procedure

The prosthesis is placed according to the instruction manual (see appendix) by an experienced knee surgeon using a standard approach and instrumentation.

5.5. The Postoperative Treatment

The patient will rehabilitate at home with help of a physiotherapist. At the regular visits at the outpatients the questionnaires will be obtained by a physiotherapist (blinded to which patient received which type of inlay). The physiotherapist was not present at the operation. The patients will complete the patient questionnaires by himself/herself. In case of a complication or adverse event, the surgeon will be called.

5.6. 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. Methods and Evaluations

Subjects will be evaluated preoperatively, prior to discharge and at follow-up intervals of 6 weeks, 3 months, 6 months, 1, 2 and 5 years. Each subject will be followed for five years post-implantation. At the 1-year follow-up a double examination will be made in order to assess the clinical RSA precision. All subject evaluations will be documented by completion of appropriate Case Report Forms (see Appendix 2).

Table 1 – Evaluation schedule (functional and patient assessment)

	Pre -op	Op	< 1wk (prior to discharge)	6wk	3m	6m	1yr	2yr	5 yr
Range (weeks)				±4d	±1wk	±2wks	±4wks	±4wks	±6ks
Demographic Information	✓								
Historical Record	✓								
Clinical Evaluation			✓	✓	✓	✓	✓	✓	✓
Operative Record		✓							
Knee Society Score	✓			✓	✓	✓	✓	✓	✓
SF-36	✓			✓	✓	✓	✓	✓	✓
EQ 5-D	✓			✓	✓	✓	✓	✓	✓
Lower-Extremities Activity	✓			✓	✓	✓	✓	✓	✓
RSA analysis			✓	✓	✓	✓	✓ **(double)**	✓	✓
Radiographic imaging	✓ **AP/**		✓ **Lat**	✓	✓ **Lat**	✓	✓ **Lat**	✓ **Lat**	✓ **Lat**

	Lat								
Adverse Events (including revision)		**Anytime**							

Basic demographic and medical history information is 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.

Prior to surgery (- 2 months)

Demographic information:	Date of birth Height/ weight Gender	
Patient's initial diagnosis		
Operative side		
Historical record	Cigarette Smoker Medical History: Concurrent Medical condition and current treatment according to medication category (ATC Class)	
Am. Knee Society Score AKSS*	Pain intensity Active and passive range of motion (Neutral-zero-method) Stability Anatomic alignment Walking/standing ability Stair climbing ability Use of walking aids	
Patient questionnaires	SF-36 EQ-5D LEAS (Lower Extremities Activity Scale)	
Radiographic assessment	Anterior/posterior Lateral	

Surgical Procedure

Anesthesia	Type ASA	
Systemic prophylactic therapy	Antibiotic	

	Anticoagulant	
Bone cement		
Surgical approach		
Soft tissue released		
Navigation		
Deviation from site-specific surgical procedure		
Bone removed	Femur Tibia Slope	
Tantalum balls (ø 1.0 mm)	Position in the tibia bone	
Time	Skin to skin Tourniquet	
Implant details	Sizes of components Product labels	
Intra-operative complications		

Assessment at on week postoperative

Clinical evaluation	Concomitant therapy	Pain medication
	Systemic prophylactic therapy	Antibiotic Anticoagulant
	Rehabilitation/mobilization	Site specific procedure Discharged
Radiographic assessment	Anterior/posterior Lateral Radiostereometric analysis	
Early post-op complications		

Follow-up assessment at 6 weeks, 3 months, 6 months, 1 year, 2 years and 5 years

Clinical evaluation	Patient status	
	Concomitant therapy	Pain medication
	AKSS*	
	Patient questionnaires	SF-36 EQ-5D
Radiographic assessment	Anterior/posterior Lateral Radiostereometric analysis	

Complications		

Termination

Date of evaluation		
Study completion	Reason for early termination	
Position of study device at last contact to patient		
Problems at last contact		

6.1. Study parameters/endpoints

6.1.1 Clinical outcome

- Relief of Pain, measured by an increase in the pain score component of the Knee Society Score
- Restoration of Function, measured by an increase in the functional score of the Knee Society Score.
- Patient satisfaction as determined by answers to patient outcomes questionnaires (EQ 5-D, SF-36 and Lower Extremity Activity Scale).

6.1.2 Durability of the device

- The absence of revisions/removal due to pain and/or loosening.
- Radiological integrity. The integrity of the implant / bone interfaces will be assessed. The occurrence of radiolucent lines / radiolucency being defined as a clearing or radiolucent line not exceeding 2 mm in width at the bone / prosthesis.
- Progressive radiolucency being defined as radiolucencies which increase no more than 2mm in two or more zones in the femoral or tibial implants.
  - Anterior-Posterior (AP) view
  - Skyline (Merchant View) at 30 degree Knee Flexion
  - Lateral View

6.1.3 Patient success or failure

Each patient from the two groups must meet the following criteria at the two-year (± 2 months) evaluation in order to be considered as “success”:

Patient Success - defined by the following requirements at the two-year follow-up interval:

- A Knee Score of ≥ 80, and
- No component revisions or removals (femoral, bearing, tibial or patella), and
- No pending component revisions or removals (femoral, bearing, tibial or patella) and
- Absence of Osteolysis in any component (femoral, bearing, tibial or patella) and
- No migration / subsidence of >3mm or >3º in any component (femoral, bearing, tibial or patella)

A patient who meets any of the following criteria at the two-year (± 2 months) evaluation will be considered as “failure”:

Patient Failure – defined by the following requirements at the two-year follow-up interval:

- A Knee Score of < 80, or
- Revisions or removals of any component (femoral, bearing, tibial or patella), or
- Pending revisions or removals of any component(femoral, bearing, tibial or patella), or
- Presence of Osteolysis in any component(femoral, bearing, tibial or patella), or
- Migration / subsidence of 3 mm or >3º in any component (femoral, bearing, tibial or patella).

6.1.4 Surgical Procedure

Standard, accepted surgical procedures for total knee arthroplasty will be utilized. The specific surgical procedure performed at the 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. Study Procedures

Patient packs containing all the necessary Case Report Forms for the duration of the study will be supplied to the PI prior to commencing the Study. Samples of the forms are included in the Report Forms section of this protocol.

An Informed Patient consent Form will be completed. Diagnosis may include any confirmatory test as deemed necessary by the surgeon, such as x-ray, CT (computerised tomography) or MRI (magnetic resonance imaging). Standard pre-operative blood and laboratory tests should be conducted.

An Operative Record will be completed to record details of each operative procedure.

6.3. The RSA Procedures

The fixation and stabilization of the tibia components will be assessed using RSA. During the surgical procedure at least three well-scattered tantalum markers are installed (ø 1.0 mm) into the bone around

the tibial component to obtain skeletal landmarks. The tantalum markers are locked inside a rotating cartridge inside a specially designed insertion instrument (Halifax Biomedical, NS, Canada).
At the routine control visits (discharge day, 6 weeks, 3, 6, 12, 24 months and 5 years), the radiographs will be taken and the physical evaluation will be performed.
The RSA data of the prostheses components will be compared in terms of subsidence, linear, and rotational movements and wear. If the prosthesis is stable and fixed the differences will be zero.
The RSA set-up consist of two synchronized roentgen tubes positioned approximately 1.5 meter above two roentgen cassettes (35*43 cm) at a 20° angle to the vertical. Both roentgen tubes simultaneously expose the roentgen film. A carbon fiber calibration box (Medis specials b.v., Leiden, The Netherlands) is used to calibrate the experimental set-up (loaned by Stryker to the hospital for the duration of the study, covered in study contract).
The RSA X-rays of the discharge day (4-7 days postoperative) is used as baseline. Since the tantalum balls are fixed in the bone around the tibial implant, the position of the implant relative to the bone can be calculated. Taking these bone markers as reference points, the spatial translations and rotations of the tibial component during follow-up can be calculated (Kaptein et al., 2006; Valstar et al. 2005). The bone markers need to be well fixated in the bone. Bone markers are defined unstable when they move more than 0.3 mm with respect to the other bone markers. Unstable markers will be excluded from analysis (Garling et al. 2005b).
For the analysis of wear the same principle can be used. Taking the tibial component as a reference, the spatial translations and rotations of the femoral component during follow-up can be calculated. The relative change in proximal – distal direction of the femur with respect to the tibia will be denoted as polyethylene wear.

7. Adverse Events

7.1. Section 10 WMO

In accordance to section 10, subsection 1of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

7.2. 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"

7.3. 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

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.

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 casual 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 casual 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.

7.4. Reporting of Serious Adverse Events and Adverse Device Events

7.4.1 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:

Annemarieke van Dam, CRA

Phone: +31 (0) 418569813

Mobile: +31 (0) 622741602

Fax: +31 (0) 418 569 777

Email: annemarieke.vandam@stryker.com

7.4.2 METC Notification by Investigator

Reports of serious adverse device effects - including follow-up information - must be submitted within 48 hours to Stryker and the accredited METC that approved the protocol, according to the requirements of that MTEC. Copies of each report and documentation of METC notification and receipt will be kept in the Investigator Site File and also in the study Master File.

7.5. 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.

7.6. 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 / Benefit 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 RSA-radiographs. The effective radiation dose per RSA-radiograph is 3 µSv (Teeuwisse *et al*., 1998). The additional annual radiation dose is negligible if the natural annual exposure of 2 mSv is considered and will do the patient no harm (Blake *et al*., 1996). The International Commission on Radiological Protection categorizes the corresponding level of risk qualitative due to radiation as 'trivial' with a quantitative risk of about one in a million or less. The required level of benefit should be related to 'only increase knowledge'. (http://ec.europa.eu/energy/nuclear/radioprotection/publication/099_en.htm)

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 polyethylene (X3, 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, girdlestone 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 well being 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

Continuous outcome variables and their differences will be analyzed with parametrical statistical techniques, such as t-tests, unless the normality assumption does not seem reasonable for the data, in which case non-parametric techniques will be considered e.g. Wilcoxon/Mann-Whitney tests.

Categorical outcome variables will be analyzed with chi-square tests and/or Fisher's exact tests (depending on the expected values in the categories). For the relevant parameters (subsidence, survival, pain and function) also the 95 percent confidence intervals will be calculated.

The effect of parameters such as age, sex and operators will be evaluated using multiple variate analysis.

All data will be analyzed by blinded researchers.

9.2. Missing Data

No imputation of missing data will be made. If any questionnaire (e.g., AKSS) 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 METC according to the local METCs reporting procedures.

Protocol Deviations for this study include the following:

- Informed consent process is not carried out according to ISO 14155 Part 1.
- 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, radiographs, 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) (see appendix 2) 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.

A sample case report form is provided in Appendix 2.

10.3. Data Management

Data will be collected (description of process see paragraph 10.1. study monitoring plan) and sent to Data Management at Stryker for entry into a database which is held at the Stryker SA offices in Montreux. 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 Conciderations

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” (Declaration of Helsinki, October 2002) (see Appendix 8) and in accordance with local regulations.

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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 is 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, and date of birth. In all data analyses the identity of patients will remain anonymous. Anonymous 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 and/or marketing 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.

11.6. Legal Approvals, Annual Progress Report and end of Study Report

11.6.1. Submission of Documents at Study Start

Before the study starts, the Clinical Investigation Plan, Informed Consent Form and any other applicable documents will be submitted to the METC 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 METC. This also applies to any communication between the investigator and the authorities.

11.6.2 Annual Progress Report

The principal investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.6.3 End of Study Report

The principal investigator will notify the accredited METC (and the competent authority) of the end of the study within a period of 8 weeks (90 days). The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the principal investigator will notify the accredited METC (and the competent authority within 15 days), including the reasons for the premature termination. Within one year after the end of the study, the principal investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC (and the Competent Authority).

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 15 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

This study is financed by Stryker SA. The financial aspects of the study will be documented in an agreement between Stryker SA 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
CRF	Case Report Form
DCF	Data Clarification Form
EC	Ethics Committee
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
METC	Medisch-ethische toetsingscommissies = Medical Research Ethics Committees
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
WMO	Wet medisch-wetenschappelijk onderzoek met mensen
	= Medical Research Involving Human Subjects Act
WOMAC	Western Ontario McMaster Osteoarthritis Index

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19. Appendices

Appendix 1 Contact Details
Appendix 2 Patient Information and Informed Consent
Appendix 3 Case report Form

Appendix 1: Contact Details

Sponsor (Project management / monitoring)

Eric H. Garling, PhD Clinical Research Manager Stryker GmbH & Co KG Dr.-Homer-Stryker-Platz 1 D-47228 Duisburg Fon: +13 (0) 646713518 Fax: +49 (0) 2065/837 419 E-mail: eric.garling@stryker.com	Annemarieke van Dam Clinical Research Associate Stryker Nederland Koeweistraat 8 4181 CD Waardenburg the Netherlands Phone: +31 (0) 418569813 Mobile: +31 (0) 622741602 Fax: +31 (0) 418 569 777 E-mail: annemarieke.vandam@stryker.com

Principle investigator

H. Kaptijn, MD
Department of Orthopaedics
't Langeland Ziekenhuis Zoetermeer