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Old Protocol Number / Version:	R3H01/01/05/2009/Version 01/BNA
Old Protocol Date	January 05, 2009
Current Protocol Number / Version:	**R3H01/02/01/2017/Version 2.0 /BNA (including Post-Approval Study of the R3 Biolox delta Ceramic Acetabular System – Europe)**
Current Protocol Date	**February 01, 2017**
Sponsor:	Smith & Nephew Orthopaedics AG Oberneuhofstrasse 10D 6340 Baar Switzerland

Investigator's Statement

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by the sponsor and ethics review board. I agree to await ethics review board approval of the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by the protocol and case report forms, and to maintain study documents for the period of time required.

Investigator Signature	**Date of Signature**

Confidential

Protocol Summary

Title of Study:	A prospective, multicenter, non-randomized, clinical outcome study of the R3 Acetabular System in patients with degenerative hip disease
Study Device:	R3 Acetabular Hip System
Indications for Use:	Degenerative joint disease
Primary Investigator:	Ville Remes, MD, PhD
Study Design:	Prospective study
Length of Study:	10 years
Number of Study Centers:	Max 8 European sites
Number of Subjects:	500
Consecutive Enrollment:	18 months
Study Objectives:	Safety and effectiveness of the R3 Acetabular System
Study Variables:	Harris Hip Score HOOS UCLA Radiographic Evaluation Adverse Events Revisions
(Post Approval Study) PAS cohort	The PAS cohort consisted of 137 subjects who were implanted with the R3 delta Ceramic Acetabular System (DoD) in the pivotal study. These patients will continue to be followed to 10 years post-operatively. The primary endpoint for the PAS study is implant survivorship at 10 years post study procedure.

Study Flow Chart/ Time and Events Schedule

Study Activity	Preop	Op	DC	3M	1Y	3Y	5Y	7Y	10Y
Inclusion/Exclusion	X								
Informed Consent	X								
Demographics/Med History	X								
Harris Hip Score	X			X	X	X	X	X	X
UCLA	X			X	X	X	X	X	X
HOOS	X			X	X	X	X	X	X
Radiographic Evaluation			X		X*	X	X	X	X
Operative Analysis		X							
Discharge			X						
Adverse Events		x	x	x	x	x	x	x	x

* Full Pelvic overview

Abbreviations

ASA	American Society of Anesthesiologists
AE	Adverse Event
AP	Anteroposterior
BRH	BIRMINGHAM HIP Resurfacing System
CAOS	Computer Assisted Orthopaedic Surgery
CAPA	Corrective and Preventive Action
CE	European Conformity
CoC	Ceramic-on-ceramic
CRA	Clinical Research Associate
CRF	Case Report Form
CXLPE	Ceramic-on-cross-linked polyethylene
DC	Discharge
DDH	Developmental Dysplasia of the Hip

DoD	Delta on Delta = BIOLOXdelta
EC	Ethic commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HOOS	Hip disability and Osteoarthritis Outcome Score
ISO	International Organization for Standardisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
ICMJE	International Committee of Medical Journal Editors
KM	Kaplan-Meier
MIS	Minimal Invasive Surgery
MoM	Metal-on-Metal
mHHS	Modified Harris Hip Score
MoP	Metal-on-Polyethylene
MoXLPE	Metal-on-XLPE
NICE	National Institute for Clinical Excellence
ODE	Office of Device Evaluation
ODEP	Orthopaedic Data Evaluation Panel
PAS	Post – Approval- Study
PE	Polyethylene
PI	Principal Investigator
PMA	Premarket Approval Application
SAE	Serious Adverse Event
SD	Standard Deviation
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
THA	Total hip arthroplasty

UCLA rating	University of California, Los Angeles
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
XLPE	Cross-linked polyethylene

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ADDENDUM I
POST-APPROVAL STUDY OF THE R3 BIOLOX DELTA CERAMIC ACETABULAR SYSTEM – EUROPE

1. Study Contact Information

Sponsor:	Smith & Nephew Orthopaedics AG Oberneuhofstrasse 10D 6340 Baar Switzerland
CRA:	See Sponsor contact list
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2. Introduction

Total hip arthroplasty (THA) is the gold standard treatment of severe hip osteoarthritis refractory for conservative treatment. THA is a common procedure. More than 25,000 primary hip procedures are performed annually in Canada[1], more than 30,000 in Australia[2], and more than 234,000 THA procedures in the United States[3]. Follow-up information for the last 30 years indicates that THA results in immediate and significant pain relief and increased functional capacity for the patient. The more recent development of patient outcome questionnaires confirms the improvement in the patient's overall quality of life due to total hip replacement[4]. The majority of patients report significant decreases in joint pain and improvements in activities of daily living by three months postoperative[5]. Historically, THA was used to treat patients in the 60-75 years of age range[6]. More recently, this age range has expanded to include older patients, as well as younger patients whose hip implants will be subjected to greater mechanical stresses for a longer period of time.

R3 Acetabular System

The R3 system was designed to provide a possibility to tailor the implant to each patients requirements. The Reflection® acetabular components, which have been used for more then 10 years, built a legacy of success on innovation and refinement. Excellent clinical long-term results have been published[7]. Critical to this success is the polished inner shell surface. The R3® Acetabular System continues this legacy by reducing wear on the back-side of the liner by utilizing this polished counter face in the refined cup design.

The R3 system is currently available with no-hole and three-hole shells with and without HA coating and its shells have a hemispherical design. For an improved primary and secondary stability the R3 has a porous coating Stiktite. This coating contains sintered asymmetric titanium grains as opposed to uniformly shaped sintered beads offered on the Reflection system. This allows for an enhanced scratch fit and stability. Stiktite coating utilizes the same sintering process as RoughCoat, it is not a sprayed application as with plasma spray. However, Stiktite is not a new coating and has been in clinical use with over 100,000 implantations by other manufacturers in orthopaedic applications under the brands K-Coat and 3-D-Matrix.

The R3 system was designed with head size in mind. The designers wanted to fit the largest head size in the smallest shell possible without compromising poly thickness. A minimum poly thickness of 5 mm in the load bearing areas is maintained. The locking mechanism allows to accommodate poly liners with a double-channel lock design that provides axial stability and 12 large anti-rotational tabs on the poly liner that provide rotational stability and a locking taper that supports metal and

ceramic liners. The push-out and torque-to-failure tests of the R3 locking mechanism demonstrate that it offers the benefit of a secure and stable liner. The R3 lock can withstand over 1112N of push-out force in any of its liner options and over 40 N-m of torque[25].

Bearing Options

Many bearings have been used over the years in hip replacement systems: Ceramic-on-ceramic (CoC), ceramic-on-cross-linked polyethylene (CXLPE), metal-on-polyethylene (MoP), metal-on-XLPE (MoXLPE), Oxinium-on-XLPE and metal-on-metal (MoM).

Ceramic on Ceramic

Ceramic on Ceramic (CoC) implant surfaces are not a new concept in THA. Ceramic bearings have been used for over thirty years in prosthetic hip components. The type of ceramic used in THA today is aluminum oxide, also know as alumina. The clinical use of ceramic as a bearing surface dates back to the early 1970's. It was developed to reduce wear in the hip joint. The improved wear characteristics of alumina ceramic can result in a longer lasting implant. The recent publication regarding CoC hip implants continue to demonstrate good performance even of early monolithic designs manufactured before modern material were available, with survival rates in some instance in excess of 80% well beyond 10 years[8].

The R3 system is offering BIOLOXforte and BIOLOXdelta (Delta on Delta = DoD) liner options in the diameters 32 and 36 mm. The unique feature about R3 ceramic liners is that they come with a titanium support ring around the periphery of the liner. The support ring and ceramic liner are precisely assembled utilizing a cold pressing process, which assures that material properties of the ceramic and titanium are not altered. The support ring offers greater protection against chipped edges and tensile forces for the ceramic insert that result in high fatigue and burst performance for insert assembly. Laboratory tests have shown that the burst strength of these liners is significantly higher than that of traditional ceramic liners without band. Based on these test results, it can be hypothesized that these liners with titanium band would reduce the incidence of fracture of the ceramic liners." There will be additional analysis as part of an Food and Drug Administration (FDA) post approval commitment for patients receiving the R3 delta Ceramic Acetabular System (see Appendix I).

Polyethylene

Polyethylene (PE) is the most understood and used of all the liner materials. Because of its durability and performance, Metal on PE (MoP) has been the leading artificial hip component material chosen by surgeons since European Conformity (CE) approval 30 years ago. Cross-linked polyethylene (XLPE) was introduced later to improve wear properties of polyethylene.

The R3 system offers four XLPE liner options – 0 degree, 20 degree, 0 degree +4 and 20 degree +4. Conventional polyethylene will not be offered. The Smith & Nephew 10 Mrad, fully annealed XLPE is the only cross-linked polyethylene proven to produce less volume of wear debris particles in all head size ranges. Less wear debris provides a chance for reduced osteolysis.

Metal-on-metal

Early experience with metal-on-metal (MoM) bearings validated the concept of this articulation surface for THA[9]. In particular, the wear properties of MoM bearings received greater attention as the limitations of MoP bearings became known. Although the long-term success of the McKee-Farrar and Ring THA systems is attributed in part to a high carbon cobalt chrome molybdenum (CoCrMo) alloy used to produce the devices in the 'as cast' metal, reasons for failures of these devices include the limitations of manufacturing methods at the time these devices were produced[10]. The newer MoM prostheses utilize improved bearing geometry and new surface finishings that promote lubrication. Mid-term follow-up on these prostheses demonstrates equivalent safety and effectiveness outcome compared to MoP prostheses[11]. They offer the potential for greatly reduced wear. Metal bearings are available in several sizes. Large femoral heads can provide increased range of motion and greater stability, which can significantly reduce the risk of hip dislocation[12].

Superior metallurgy and optimal clearances, also used in the clinically proven, highly successful, world-leading BIRMINGHAM HIP Resurfacing System (BHR), provide the R3 Metal-on-Metal system superior performance. The R3 Metal-on-Metal and the

BHR system utilize high-carbide cobalt chrome in the as-cast micro-structural condition, providing superior wear resistance. The R3 provides specific metal inserts for large femoral head sizes (Ø38mm – 54mm heads in shell sizes 50mm – 68mm) which are either combined with the modular BHR heads or the BHR resurfacing.

3. Study Objective

The objective of this study is to determine the long-term safety and effectiveness of the R3 Acetabular System

Hypothesis: implant survivorship (Kaplan-Meier) (revision for any reason) of the R3 cup is at least 97% at 3 years, 95% at 5 years, 93% at 7 years, and 90% at 10 years follow-up.

3.1. Study Design

This is a multicenter prospective observational post-market clinical follow-up study that will include 500 patients who will have total hip replacement with the R3 Acetabular System and either cemented or cementless hip stem.

3.2. Sample size

The target enrolment during this study is 500 patients. This number of patients leads to representative results with a greater precision of the survival rates, i.e. small confidence intervals.

The sample size is large enough to satisfy pseudo-regulatory requirements set-forth in individual European countries such as the Orthopaedic Data Evaluation Panel[13] (ODEP) and the National Institute for Clinical Excellence (NICE) requirements[14]. According to the ODEP criteria for categorizing products in relation to NICE's long-term benchmarks for hip replacements, a level A study (strongest evidence) requires an initial cohort of 500 patients or more.

4. Outcome Measures

4.1. Effectiveness Measures

Effectiveness will be assessed by comparison of changes in parameters contained in the Hip disability and Osteoarthritis Outcome Score (HOOS) questionnaire[15] and based upon incidence of revision and change in Harris Hip Score[16] and University of California, Los Angeles (UCLA) Rating[17].

4.2. Safety Measures

Safety will be measured by assessing all adverse events experienced by patients related or probably related to the study device. Adverse events will be documented at the intra-operative and all postoperative evaluation intervals to determine the safety profile of the device. The incidence of surgery- and device-related events such as device revision, component failure, malfunction, migration, subluxation, dislocation, loosening, nerve damage, deep infection, deep vein thrombosis, pulmonary embolism, or bone breakage/fracture will be collected. Some events may not be evident until after a long-term follow-up such as evidence of severe osteolysis, excessive articular surface wear, or significant debris production. All adverse events in study patients between enrollment and ten years shall be reported at the time of occurrence. Efficacy and safety measurement will be performed as summarized in the study schematic presented in Table 1.

5. Study Population

This clinical study can fulfill its objectives only if appropriate subjects are enrolled. All relevant medical and non-medical

conditions should be taken into consideration when deciding whether a particular patient is suitable.

5.1. Subject Inclusion Criteria

Subjects must meet all of the following characteristics for inclusion in the study.

- Patient is 18-75 years old and he/she is skeletally mature
- Patient requires primary total hip arthroplasty due to non-inflammatory degenerative joint disease (e.g. osteoarthritis, post-traumatic arthritis, avascular necrosis, dysplasia/DDH or inflammatory joint disease (e.g., rheumatoid arthritis)
- Patient has met an acceptable preoperative medical clearance and is free from or treated for cardiac, pulmonary, hematological, etc., conditions that would pose excessive operative risk
- The patient is willing to comply the follow-up schedule

5.2. Subject Exclusion Criteria

Subjects with any of the following characteristics must be excluded from the participation in the study.

- Patient has active infection or sepsis (treated or untreated)
- Patient is a prisoner or has an emotional or neurological condition that would pre-empt their ability or unwillingness to participate in the study including mental illness, mental retardation, linguistic insufficiencies (i.e. immigrants), or drug/alcohol abuse.
- Patients with acute hip trauma (femoral neck fracture)

To enroll a patient in the study he/she needs to meet all the inclusion criteria and none of the exclusion criteria.

5.3. Recruitment Procedure

Patients will be enrolled consecutively. Following the recommendations of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement[18], the study will report numbers of individuals at each stage of study—eg. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed (see figure 1). The "Intention-To-Treat" (ITT) principle will be followed: once a patients has consented study participation, he or she will be considered as study subject, even if the patient did not receive the planned therapeutic treatment.

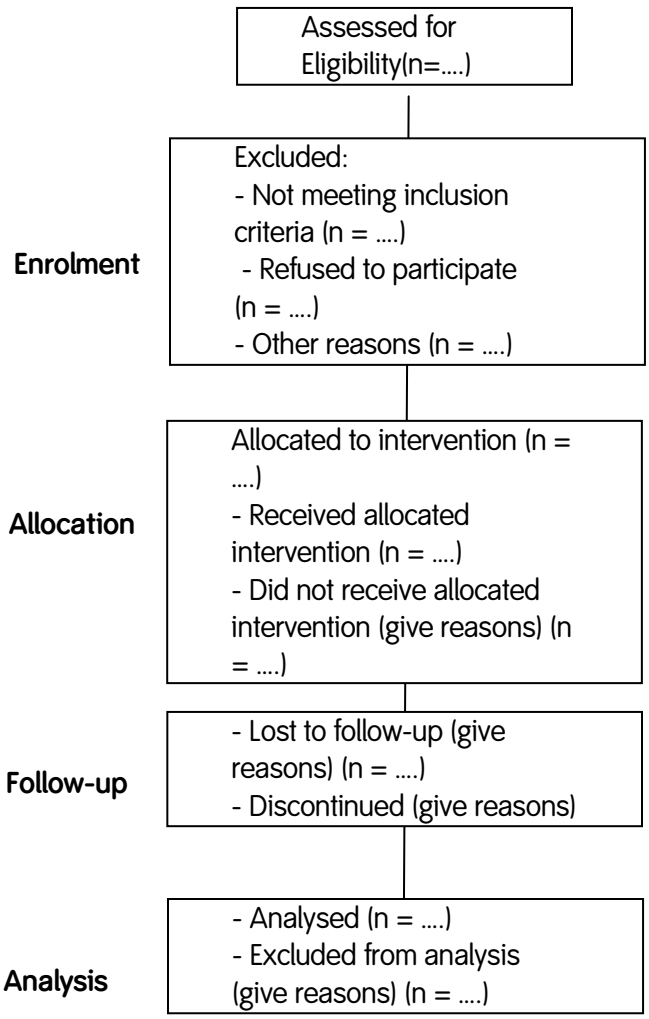

Figure 1

5.4. Informed Consent

Informed consent shall be obtained from all study participants according to ISO14155 guidelines and all applicable national regulations. Potential patients must be informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written consent form. The patient shall have sufficient opportunity to consider participation in the study; a patient cannot be led to believe that they are waiving their rights as a subject or the liability of the sponsor or investigator. Patients are then invited to sign and date the consent form, indicating their consent for enrollment. Once a patient has signed and dated the consent form, they are considered a subject of the study. The investigator will retain the original copy of the signed consent form in the study files. A duplicate copy shall be provided to the patient.

5.5. Subject Withdrawal / Termination Criteria

Whilst subjects are free to withdraw from the study at any time. All reasonable efforts should be made to retain the subjects for the 10-year duration of this study.

Study Site Discontinuation

A specific study site in this multicenter study may also warrant termination under the following conditions:

- non-compliance to Good Clinical Practice (GCP) or protocol
- major protocol deviations
- inaccurate or incomplete data
- unsafe or unethical practices
- safety or performance considerations
- investigator involuntarily discontinues participation in study

Documentation of withdrawn and lost to follow-up patients

Some actively enrolled subjects will not return for follow-up exams due to a variety of reasons. Study personnel will make all reasonable efforts to contact the subject and document the following contact attempts prior to declaring a subject to be lost to follow-up: the subject has been contacted according to the study sites policies, but no less than 2 documented phone contacts attempts and 1 letter without response. Copies of all attempts to reach the subjects per regular mail or email and/or the attempts to contact the subject via other means should be documented and kept with the subjects Case Report Form (CRF). A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for 2 consecutive visits and study personnel are unable to contact the subject. For all cases (withdrawn and lost to follow-up), information will be obtained on the Study Termination Form, detailing circumstances leading to the withdrawal.

Sites will be requested to contact non-respondent patients using phone calls, regular mail, e-mail, certified letters or other means to urge patients to return to a clinic for follow-up or ascertain if a patient has moved.

6. Medical Devices

6.1. Device Components

The subject device hip system is consisting of R3 acetabular cups and three liners: metal, ceramic and XLPE. The modular femoral heads mate with existing, commercially-available Smith & Nephew Orthopaedics uncemented or cemented femoral stems.

6.2. Surgical Technique

The medical device will be implanted using standard surgical technique, depending on the investigator's standard procedure. Instrumentation specific for the device will be used. A surgical technique brochure for implanting the acetabular cup and femoral modular heads/sleeves will be provided to each investigator. Separate surgical technique brochures are available that are specific for the stem that will be used with the modular heads.

Soft tissues should be repaired after surgery in order to minimize the risk of limping and dislocation.

Surgery performed by residents and by utilizing Computer Assisted
Orthopaedic Surgery (CAOS) or minimal invasive surgery (MIS) technique will be allowed. Use CAOS or MIS and surgery performed by residents will be documented in CRFs for further analysis.

There will not be any standard protocol for antibiotic or thrombo-embolic prophylaxis. However, all sites are encouraged to follow-up the same prophylaxis protocol during the enrolment period.

7. Treatment and Follow-up Evaluations

7.1. Schedule of Events

The intervals and schedule of events is provided in **Table 1**.

Study Activity	Preop	Op	DC	3M (+14d)	1Y (+2m)	3Y (+3m)	5Y (+6m)	7Y (+6m)	10Y (+6m)
Inclusion/Exclusion	X								
Informed Consent	X								
Demographics/Med History	X								
Harris Hip Score	X			X	X	X	X	X	X
UCLA	X			X	X	X	X	X	X
HOOS	X			X	X	X	X	X	X
Radiograph Evaluation			X		X*	X	X	X	X
Operative		X							
Discharge			X						
Adverse Events		x	x	x	x	x	x	x	x

* Full pelvic overview

7.2. Preoperative Evaluation

Information will be collected on the study population prior to device implantation. Demographic factors including age, gender and primary diagnosis will be obtained. Preoperative clinical status will be determined through a clinical evaluation. The Harris Hip Score[16], the HOOS questionnaire[15] and the UCLA Rating[17] will be collected for all patients.

7.3. Operative-Discharge Evaluation

Information on the operative procedure for each subject including surgical approach, component size, surgical time, and intraoperative blood loss and patients' American Society of Anesthesiologists (ASA) score[19] will be obtained. Additionally length of hospital stay and discharge to home or any other institution will be recorded. Any operative complications, both during the operation and prior to discharge will be collected. Any complication device-related, surgery related or otherwise will be collected.

Patients will have radiographs taken after implantation (before discharge) from the hospital to establish a baseline.

Postoperative patient mobilization is will be conducted according to the clinic's standard protocol.

7.4. Postoperative Follow-up Evaluations

Subjects will be seen at the 3 months, 1 year, 3 years, 5 years, 7 years and 10 years interval post surgery. The Harris Hip Score will be collected and the HOOS and UCLA questionnaire obtained at each visit.

Anteroposterior (AP) and (shoot trough) lateral radiographs of the operated hip will be taken before discharge in addition to at 1 year, 3 years, 5 years, 7 years and 10 years postoperatively. At least the 1 year follow-up radiograph should include full pelvic overview (including at least 20 cm of the proximal femur). Pelvic AP radiograph will be used for analysis of cup inclination and leg length discrepancy.

Postoperative radiographs will be taken to determine component alignment, radiolucencies[20,21], and bone condition. The alignment of the femoral prosthesis will be measured as the angle between the central axes of the proximal femoral canal and the femoral prosthesis. Angles will be classified as varus, valgus or neutral[22]. The angle of the acetabular cup will be

assessed by measuring the angle of vertical tilt of the acetabular cup (angle between a line joining the ischial tuberosities and one through the long axis of the ellipse of the acetabular cup)[23]. Additionally, the cup anteversion will be recorded. Observations will be recorded on the x-ray case report form and independently reviewed.

7.5. Telephone Follow-Up

If subjects are unable to return for follow-up visits to the investigator's office, they may be contacted by telephone to assess their status. Subjects will be asked whether the study device is in place or has been revised, and patient satisfaction will be assessed. This information will be recorded on the corresponding CRF.

8. SAFETY REPORTING

An adverse event assessment will be conducted at each follow-up interval. Data from each visit will be recorded on the study CRFs. All adverse events, regardless of their relationship to the study device, occurring from the time of study device implantation through to study completion should be recorded on the appropriate CRFs and reported as below.

8.1. Definitions for safety reporting

A. Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study medical device.

B. Serious Adverse Event (SAE)

A SAE is any adverse event that:

- resulted to death,
- was life threatening (at the time of the event); or
- resulted in hospitalization (initial or prolonged); or
- resulted in a disability or permanent damage (a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life);or
- resulted in a congenital anomaly or birth defect; or
- required medical or surgical intervention to preclude permanent impairment of a body function or prevent permanent damage to a body structure; or
- does not fit the other outcomes above, but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

C. Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

The Investigator will assess and categorize AEs as mild, moderate or severe based on the following definitions:

- Mild: the subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or wellbeing.
- Moderate: the subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or wellbeing and may require medical intervention and/or close follow-up.
- Severe: the adverse event interferes considerably with the subject's usual activities. The event is of definite

concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

The Investigator is responsible for assessing the relationship of the AE to the study device and study procedure based on the following definitions:

- Unrelated: the event is clearly not related to the study device or study procedure
- Possible: the event may or may not be related to the study device or study procedure. A relationship cannot be ruled out.
- Probable: the event is likely related to the study device or study procedure. A relationship cannot be ruled out.
- Definite: the event is clearly related to the study device or study procedure.

D. Reoperation and Revisions

A reoperation is any surgical procedure of the study hip. A revision is a surgical procedure of the study hip where one or more of the study components are removed and replaced with new implants.

All reoperations and study component revisions should be documented on the Adverse Event CRF.

8.2. Investigator's Responsibilities

All reportable adverse events that occur during this follow-up phase should be fully documented in the research record by the Investigator including the onset date, complete description of the event, severity, seriousness, duration, action taken and outcome. Additional information on these events may be required. The event should be documented on the Adverse Event case report form. The investigator will be responsible for notifying the reviewing Ethics Committee (EC) / Investigational Review Board (IRB), and if applicable other authorities, of any reportable adverse events according to local regulations.

Adverse events which are possibly, probably, or definitely related to the device must be reported promptly to the sponsor. Adverse events which are unanticipated (UADE) must be reported to the sponsor by telephone or by email as soon as possible, and the completed Adverse Event CRF must be faxed to the Sponsor within 10 working days of gaining knowledge of the event together with a cover letter describing the event and detailing the medical history. The investigator shall also supply a copy of the completed Adverse Event form, together with a cover letter describing the event and detailing the medical history to the Ethics Committee. The investigator will also provide any relevant follow-up information and the outcome of the event as soon as possible.

Safety reporting: Sponsor's Responsibilities

Sponsor will provide progress reports on safety events to the Investigator to report to the EC / IRB as required. The Sponsor will also determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

8.3. Explantations

In the short term, explantations will usually occur due to acute/chronic infection, instability, and/or subject experiencing severe pain due to various causes. Reduced mobility alone, if it occurs, is typically not a predominant factor in prompting revision surgery. Long-term, aseptic loosening and/or severe pain may become a determining factor as to whether to proceed with device revision. Reasons for removal are not limited to these circumstances alone. The Sponsor requests Investigators to return any revised R3 Hip System components for retrieval analysis.

Explanted components are sterilized by steam autoclave or other appropriate sterilization method according to the Institution's standard sterilization procedures. Only properly packaged explants should be shipped, and the Sponsor notified before any shipment. If possible, the Sponsor will collect histological (bony ingrowth quality, bone quality, response to potential wear debris, etc.) and metallurgical (metal wear, deformation, cracking, corrosion, etc.) information from explants. For all explants, the investigator must record and forward a description of intra-operative findings including: 1) presence of

wear debris, 2) what types of hip components are being replaced, 3) and intraoperative findings relating to the device failure. Explant analysis will occur through the duration of this study.

It should be noted that the Sponsor is not always able to retrieve known explants. Some surgeons may refuse to return explants, and some institutions/hospitals will not release explanted component(s) due to their "policies."

9. Statistical Methods

Evaluations after database closure will be performed on an Intention to Treat (ITT) basis. The analysis will include the descriptive statistics of patient demographics and baseline characteristics. Accountability data will include the number of patients enrolled and the follow-up data collected. Data will be analyzed for changes from preoperative at 3 months, 1 year, 3 years, 5 years, 7 years and 10 years. Safety will be assessed by identifying and summarizing device-related adverse events throughout the study. Analysis of the success rate will be performed using Kaplan-Meier (KM) Survival Analysis. The KM estimate of the success rate along with the 95% confidence interval of the estimate will be included in the final report.

Multiple imputation techniques will be used to cope with missing data. Under the general conditions of missing at random and missing completely at random, multiple imputation result in unbiased estimates of study associations and correctly estimated standard errors and confidence intervals[24].

10. Monitoring Procedures

10.1. Source Documentation

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject (source documents). Examples of source documents are: hospital records, clinic and office charts, x-rays, and research subject files.

10.2. Direct Access

This study may be monitored by the Sponsor or a qualified person designated by the Sponsor. This qualified person could be an employee of the Sponsor or of a contract research organization (Sponsor's agent). The investigator will provide Sponsor, Sponsor's agents, EC / IRB and regulatory agencies with direct access to all source data/documents to permit study-related monitoring, audits, EC / IRB review, and regulatory inspections.

10.3. Interim Monitoring Visits

A clinical monitor, whether an employee of the Sponsor or its designee, has the obligation to follow this study closely. In doing so, the monitor will, in addition to maintaining necessary contact with the study site, visit the study sites at periodic intervals according to a schedule determined by the Sponsor.

10.4. Sponsor Audits and Regulatory Inspection

Quality assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format.

10.5. Closeout Visit

A study close out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries, and review regulatory requirements regarding records retention and EC /IRB reporting requirements.

All activities associated with a visit (Interim Monitoring, Close out) will be documented by the monitor.

11. Data Handling and Record Keeping Requirements

Case report forms (CRFs) have been supplied by the Sponsor. Subjects will be identified by a study number and subject identification code. Only the Investigator site will have the key to identify individual subjects.
The Investigator is responsible for the timely and accurate completion of CRFs. All documents related to the study must be securely archived at the study site or in a central archive.
Data required according to this protocol are to be recorded on the case report forms(CRFs) at the time of the scheduled visits. Once a subject is enrolled, completed CRFs should be sent to the Sponsor, either by fax or by e-mail, as soon as possible.

Clinical research records shall be stored in a manner that ensures privacy, confidentiality, security and accessibility of the records both during and after the conduct of the study. The Investigator/Institution will take measures to prevent accidental or premature destruction of those documents. The investigator must retain essential study documents for at least 2 years after the latest of the following: the date the study is terminated or completed or the date the documents are no longer needed to support a premarket approval application. If the Investigator needs to dispose of the documents, the Sponsor should be contacted for approval prior to disposal or destruction. The investigator will retain these documents for a longer period if required by the applicable local laws. If the responsible investigator retires, relocates, or withdraws from responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

12. DEVIATIONS FROM PROTOCOL

A protocol deviation is an instance of failure, intentionally or unintentionally, to follow the requirements of the protocol. Protocol deviations include, but are not limited to: study visits outside the window or missed, failure to capture patient reported outcomes using the Modified Harris Hip Score (mHHS) at defined time points, failure to conduct radiologic evaluation at defined timepoints, failure to collect adverse events at defined time points, and failure to withdraw subjects defined by protocol withdrawal measures.

12.1. Protocol Deviation Reporting Requirements

Deviations must be reported to the Sponsor as soon as reasonably possible. When protocol deviations affect the scientific soundness of the study, or the rights, safety or welfare of the study subjects, the Investigator may also need to report protocol deviations to the EC of the study site. It is the responsibility of the Principal Investigator (PI) to inform the IRB / EC of the deviation, per local requirements.

Investigators and all study staff (staff at site and at Sponsor) are responsible for ensuring adherence to study protocol. During the monitoring visits, the Sponsor representative will review all deviations with the Investigator. If a deviation is discovered outside of a monitoring visit, it should be evaluated via phone, email or letter. Appropriate measures to address the occurrence, additional monitoring visits, or audit of the study should be taken, which may include defining and implementing a Corrective and Preventive Action (CAPA).

13. Reports

Annual reports will be prepared and submitted to the EC / IRBs per the local requirements and in accordance with on-going approval requirements.

The total duration of the study is 10 years from the last subject entered. Once all of the study data is collected and the database is closed for analysis, it is anticipated that the data analysis and the preparation of a final study report will take three (3) months to complete.

14. Publication policy

14.1. Multicenter Publication

The sponsor may invite the investigator to participate in a multicenter publication of the study results, in which case it will be ensured that the documents submitted for publication comply with the publisher's requirements for authors and contributors. If the publisher has no such requirements, it will be ensured that the publication meets the authorship and contributorship requirements as stated in the current Smith & Nephew Global Policy and Procedure relating Scientific Disclosures. Also, the sponsor will select a publisher based on mutual agreement with the investigators, who are invited to participate in the publication.

Investigator Publication

The investigator may publish his/her own data subject to the following restrictions:

- the multicenter manuscript must be published prior to investigators publishing their own data;
- the manuscript shall be submitted to the Sponsor for review prior to submitting the manuscript for publication;
- the manuscript must reference the study multicenter manuscript.

15. Authorship

The sponsor may invite the investigator to participate in a multicenter publication of the study results. The sponsor will select a publisher based on mutual agreement with the investigators who are invited to participate in the publication. Unless otherwise required by the journal of publication or the forum in which a presentation is made, authorship will comply with International Committee of Medical Journal Editors (ICMJE) current Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. ICMJE recommends that authorship be based on the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and
- Drafting the work or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

Subject to a publisher's copyright, Site and/or Investigator will own the copyright on publications and other copyrightable material produced as a result of the Study.

16. Protocol Amendments

It will be necessary to obtain FDA and EC / IRB approval prior to implementation of any change in the protocol that may affect the scientific soundness or the rights, safety, or welfare of the subjects involved. Notification shall be submitted to the EC / IRB of the study site by the Investigator.

17. Risk – Benefit Analysis

A. Study Related Risks

Possible risks that may occur as a result of long term follow-up study participation are:

- Subjects will be asked to return to their doctor for follow-up visits at 5, 7 and 10 years and undergo an evaluation to assess their pain and function; however, these are not interventional procedures and are not expected to add significant time to any appointments.
- This study involves the use of x-ray evaluation. X-ray exposure is cumulative over a lifetime and total exposure should be kept to a minimum. However, if the x-ray exposure when participating in the study is equivalent to the exposure the subject would receive if they chose not to participate in the study, there is no additional risk associated with this study.
- As a result of participating in the study there could be a risk of loss of protected subject information confidentiality. All applicable confidentiality standards and data protection and privacy laws will be followed by the Sponsor to ensure that data collected is handled in confidence. Data will be coded and handled only by appropriately qualified and authorized personnel.

B. Study Related Benefits

Because the surgery and all the follow-up visits are the same as when the subject would not participate in this study, there are no additional medical benefits associated by participating in this study. The information gained from this study may help improve the treatment of people that need to undergo total hip replacement.

18. Applicable norms and guidelines

Clinical Investigation: ISO 14155:1 and ISO 14155:2
Reporting: STROBE: Strengthening the Reporting of Observational Studies in Epidemiology)

19. References

1. Canadian Institute for Health Information. 2005.

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25. Internal Smith & Nephew testing on file.

ADDENDUM I

Post-Approval Study of the R3 Biolox delta Ceramic Acetabular System – Europe

Protocol Number:	R3H01/02/01/2017/Version 2.0 /BNA / 16-4049-15
Old protocol Date:	February 01, 2017
Old protocol Version:	0.3
New protocol Date:	**February 01, 2017**
New protocol Version:	**2.0**
Study Product Name:	R3 delta Ceramic Acetabular System
Sponsor:	Smith & Nephew Orthopaedics AG
	Oberneuhofstrasse 10D
	6340 Baar
	Switzerland

Table of Contents

ABBREVIATIONS & DEFINITIONS

AE	Adverse Event
ADE	Adverse Device Effect
AP	Anteroposterior
CAPA	Corrective and Preventive Action
CoC	Ceramic-on-ceramic
CoP	Ceramic-on-polyethylene
CRO	Contract Research Organization
CRF	Case Report Form
DOD	Biolox delta ceramic on ceramic
EC	Ethics Committee
EU	European Union
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HHS	Harris Hip Score
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
MoP	Metal-on-polyethylene
PI	Principal Investigator
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
THA	Total Hip Arthroplasty
THP	Total Hip Prosthesis
USADE	Unanticipated Serious Adverse Device Effect
XLPE	Cross Linked Polyethylene

Protocol Synopsis:

Title of Study:	Post-Approval Study of the R3 Biolox Delta Ceramic Acetabular System –Europe
Study Type:	Post-market Outcomes Study
Study Device:	R3 delta Ceramic Acetabular System
Indications	The R3 Ceramic Acetabular System is indicated for use in skeletally mature patients requiring primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis.
Study design:	Prospective, multicenter, observational study
Primary Endpoint:	The primary endpoint is implant survivorship at 10 years post procedure.
Secondary Endpoints:	Secondary endpoints include patient satisfaction measured by clinical assessment of pain and function and a radiographic evaluation.
Length of Study:	Subjects will be followed to the 10-year postoperative interval.
Number of Sites:	Five (5) sites
Sample Size:	135 subjects
Inclusion Criteria:	Subjects who met all inclusion criteria and none of the exclusion criteria for inclusion of their records in the PMA Cohort presented in the R3 Biolox delta Ceramic Acetabular System PMA clinical report (Subjects in the DOD treatment arm of the PMA Cohort) will be included in this PAS.
Exclusion Criteria:	Subjects in any of the other treatment arms of the original European Post-market Study are excluded from this PAS.

1. BACKGROUND AND STUDY RATIONALE

1.1. Background

Smith & Nephew Orthopaedics is the sponsor of a prospective, multicenter, non-randomized, clinical outcomes study of the R3 delta Ceramic Acetabular System in patients with degenerative hip disease in Europe. The study was designed to evaluate the performance of the R3 cup with multiple articulation couples including the Biolox delta ceramic-on-ceramic (DOD) and the Oxidized Zirconium-on-crosslinked polyethylene (OxZr/XLPE) articulation couple. The study devices were commercially available in Europe at that time, and the study satisfied EU post-market surveillance requirements. The study was conducted in compliance with ISO 14155 and International Conference on Harmonization Good Clinical Practice (ICH GCP) Guidelines (Notes for Guidance on GCP CPMP/ICH/135/95); National Statement on Ethical Conduct in Research Involving Humans, consisting of a series of Guidelines made in accordance with the National Health and Medical Research Council Act 1992; World Medical Association Declaration Of Helsinki - Ethical Principles for Medical Research Involving Human Subjects October 2008; and 21 CFR 812 revised April 1st, 2008 (Medical Devices), as well as with all applicable local laws and regulations.

Clinical data from this study was used to support a Premarket Approval Application (PMA) that was submitted to the US FDA in August 20, 2015. In the PMA, only data on DOD and OxZr/XLPE subjects were included. Approval was sought for the DOD cohort. The PMA (P150030) was reviewed by the FDA and approved on October 17, 2016. A condition of the approval was that long term follow-up data to the 10-year postoperative interval for the enrolled DOD cohort subjects continue to be reported to the FDA. The original study protocol already included a requirement for subject follow-up to the 10-year postoperative interval, thus no protocol revision of the original study was required. The post-approval study protocol of the DOD cases described in this document describes the long-term follow up requirements included in the original study, and addresses the FDA's requirements for post-approval reporting of clinical study results. Subjects in this post-approval study have already signed informed consent forms agreeing to be followed to the 10-year postoperative interval. No additional consenting is required. Study data for these subjects up to, and including, 3-year follow-up results has already been reviewed in the PMA and is not part of this protocol. The follow- up requirements to the 10-year postoperative interval in the original study protocol have been reviewed and approved by the participating study sites' Ethic Committees (EC). No new subjects will be enrolled. Study data will continue to be collected on the original study's case report forms (CRF).

1.2. Study Rationale

This study is being conducted to comply with FDA requirements of post-market surveillance of the R3 delta Ceramic Acetabular System.

2. STUDY OBJECTIVES

The primary objective of this phase of this study is to confirm that the safety and effectiveness of the R3 Biolox delta Ceramic Acetabular System (DOD) is maintained in the long term (to 10 years).

2.1. Primary Endpoint

The primary endpoint is implant survivorship at 10 years post study procedure.

The KM survivorship estimate for the DOD group in the PMA cohort at 3 years is 99.3% (95%CI: 97.4%-100.0a). Since this Post-Approval Study (PAS) is intended to document the long-term survivorship of the DOD treatment group only and no comparison to a control is required, no formal statistical hypothesis testing will be conducted.

2.2. Secondary Endpoints

Secondary endpoints include the following:

- Patient outcomes as measured using the modified Harris Hip Score;
- Radiographic evaluation to assess radiographic success defined as:
    - No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones; and
    - No femoral or acetabular subsidence greater than or equal to 5mm from baseline; and
    - No acetabular cup inclination changes greater than 4 degrees (4°)

3. STUDY DESIGN

This is a prospective, multicenter, observational study that is currently in the follow-up data collection phase. Five of the seven study sites that contributed data to the PMA cohort will participate in this PAS. The two sites that will not participate in the PAS did not enroll any R3 Biolox delta Ceramic Acetabular System (DOD) PMA subjects, as such their data is not suitable for this PAS. The DOD treatment arm of the PMA Cohort included 137 DOD subjects.

Of the 137 DOD subjects included in the PMA Cohort, one died and one was revised by the 3-year follow-up interval. A total of 135 subjects are therefore eligible for this PAS study and all attempts will be made to continue follow-up on all subjects through the 10-year postoperative interval. Telephone follow-up for determination of device survival or revision status, and patient satisfaction in cases where subjects fail to return for follow-up visits will be conducted.

4. STUDY DEVICE

The R3 delta Ceramic Acetabular System is a ceramic-on-ceramic hip prosthesis composed of modular components that include an R3 porous coated acetabular shell, alumina ceramic acetabular shell liner, an alumina ceramic femoral head, and one of four titanium alloy femoral stems. This acetabular system is used in combination with one of four titanium alloy femoral stems to comprise a total hip replacement. All implantable devices are for single use.

5. STUDY POPULATION

5.1. Subject Enrollment

All study sites and subjects have been recruited and enrollment is closed. DOD cohort subjects that were included in the PMA will continue to be followed as per the follow-up schedule established in the European Post-market Study until they reach the 10-year postoperative interval. Site agreements and signed patient informed consents are already in place and allow for the long-term data collection to 10 years proposed in this PAS.

5.2. Subject Inclusion Criteria

Subjects who met all inclusion criteria and none of the exclusion criteria for inclusion of their records in the PMA Cohort presented in the R3 Biolox Delta Ceramic Acetabular System PMA clinical report (subjects in the DOD treatment arm of the PMA Cohort) will be included in this PAS.

The inclusion criteria for the original European Post-market study are provided below for reference.

- Patient is 18-75 years old and he/she is skeletally mature
- Patient requires primary total hip arthroplasty due to non-inflammatory degenerative joint disease (e.g. osteoarthritis, post-traumatic arthritis, avascular necrosis, dysplasia/ developmental dysplasia of the hip) or inflammatory joint disease (e.g., rheumatoid arthritis)
- Patient has met an acceptable preoperative medical clearance and is free from or treated for cardiac, pulmonary, hematological, etc., conditions that would pose excessive operative risk
- The patient is willing to comply the follow-up schedule

All subjects included in the PMA cohort were required to have signed study informed consent forms, and have device labels confirming the implants used for surgery.

5.3. Subject Exclusion Criteria

Subjects in any of the other treatment arms of the original European Post-market Study are excluded from this PAS.

The exclusion criteria for the original European Post-market study are provided below for reference.

- Patient has active infection or sepsis (treated or untreated)
- Patient is a prisoner or has an emotional or neurological condition that would pre-empt their ability or unwillingness to participate in the study including mental illness, mental retardation, linguistic insufficiencies (i.e. immigrants), or drug/alcohol abuse,
- Patients with acute hip trauma (femoral neck fracture)

Additional exclusion criteria for DOD subjects in the PMA cohort:

- Any subject in the DOD arm who was implanted with any hip system component (other than the ceramic acetabular liner) that is not US FDA 510(k) cleared for use with the study ceramic head.

6. STUDY PROCEDURES

6.1. Study Schematic

The PAS follow-up intervals and schedule of evaluations are provided in Table 1. Data to the 3-year postoperative interval was included in the PMA and is indicated as already collected. Since subjects have already consented to participation to the 10-year interval, data collection is in process and on-going.

Table 1.

Study Activity	Preop	Intra -	D/C	3M	1Y	3Y	5Y (± 6 Mo)	7Y (± 6 Mo)	10Y (± 6
Inclusion/exclusion	Already collected								
Informed consent	Already collected								
Demographics	Already collected								
Modified Harris Hip Score (mHHS)	Already collected						x	x	x
Radiographic Eval	Already collected						x	x	x
Adverse Events	Already collected						X	X	X

6.2. Postoperative 5-, -7, and 10-Year Visits

At the 5-year, 7-year and 10-year postoperative visits subjects will be evaluated using the modified Harris Hip Score (mHHS). The mHHS includes a modification to the "Distance Walked" section of the Harris Hip Score to replace the number of blocks with actual distances since the term "blocks" is not commonly used as a measurement of distance in Europe.

AP and lateral radiographs will be taken at the 5-year, 7-year and 10-year postoperative visits. Radiographs will be evaluated by an independent evaluator according to a Smith & Nephew R3 Acetabular Hip Study Image Evaluation Protocol included in Appendix I.

An adverse event assessment will be conducted at each follow-up interval. Data from each visit will be recorded on the study CRFs (Appendix II).

6.3. Telephone Follow-Up

If subjects are unable to return for follow-up visits to the investigator's office, they may be contacted by telephone to assess their status. Subjects will be asked whether the study device is in place or has been revised, and patient satisfaction will be assessed. This information will be recorded on the corresponding CRF.

7. SUBJECT COMPLETION AND DISPOSITION

7.1. Enrolled Subject

All subjects have been enrolled and signed an EC approved study informed consent that described follow-up to the 10-year postoperative interval. No additional enrollment will occur.

7.2. Conditions for Study Termination

All reasonable efforts should be made to retain the subjects for the 10-year duration of this study. If the subject has a revision of any component, the subject will be terminated from the study.

A. Voluntary Withdrawal

Study participation is voluntary and subjects may withdraw at any point during the study without giving their reason for doing so. A study termination form will be completed for all subjects who do not finish the study, to document the reason for the withdrawal in the CRF.

B. Lost to Follow-Up

Some actively enrolled subjects will not return for follow-up exams due to a variety of reasons. Study personnel will make a reasonable effort to contact the subject and document the following contact attempts prior to declaring a subject to be lost to follow-up: the subject has been contacted according to the study sites policies, but no less than 2 documented phone contacts and 1 certified letter without response. Copies of all attempts to reach the subjects per regular mail or email and/or the attempts to contact the subject via other means should be documented and such documentation should be kept with the subjects CRF. A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for 2 consecutive visits and study personnel are unable to contact the subject.

C. Study Termination by Investigator/Sponsor

The Investigator **may** withdraw subjects from the study for many reasons, including but not limited to the following:

- subject noncompliance to study schematic
- subject lost to follow-up

The Investigator **should** withdraw subjects from the study:

- in case any component of the original hardware is revised/exchanged
- if the Investigator or the Sponsor stops the study for any reason

For each case, information will be obtained on the Study Termination Form, detailing circumstances leading to the withdrawal.

D. Study Site Discontinuation

A specific study site in this multicenter study may also warrant termination under the following conditions:

- non-compliance to Good Clinical Practice (GCP) or protocol
- major protocol deviations
- inaccurate or incomplete data
- unsafe or unethical practices
- safety or performance considerations
- investigator involuntarily discontinues participation in study

8. SAFETY REPORTING

All adverse events, regardless of their relationship to the study device, occurring from the time of study device implantation through to study completion should be recorded on the appropriate CRFs and reported as below.

8.1. Definitions for safety reporting

A. Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the study medical device.

B. Serious Adverse Event (SAE)

A SAE is any adverse event that:

- resulted to death,
- was life threatening (at the time of the event); or
- resulted in hospitalization (initial or prolonged); or
- resulted in a disability or permanent damage (a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life);or
- resulted in a congenital anomaly or birth defect; or
- required medical or surgical intervention to preclude permanent impairment of a body function or prevent permanent damage to a body structure; or
- does not fit the other outcomes above, but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

C. Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

The Investigator will assess and categorize AEs as mild, moderate or severe based on the following definitions:

- Mild: the subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or wellbeing.

- Moderate: the subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or wellbeing and may require medical intervention and/or close follow-up.
- Severe: the adverse event interferes considerably with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

The Investigator is responsible for assessing the relationship of the AE to the study device and study procedure based on the following definitions:

- Unrelated: the event is clearly not related to the study device or study procedure
- Possible: the event may or may not be related to the study device or study procedure. A relationship cannot be ruled out.
- Probable: the event is likely related to the study device or study procedure. A relationship cannot be ruled out.
- Definite: the event is clearly related to the study device or study procedure.

D. Reoperation and Revisions

A reoperation is any surgical procedure of the study hip. A revision is a surgical procedure of the study hip where one or more of the study components are removed and replaced with new implants.

All reoperations and study component revisions should be documented on the Adverse Event CRF.

8.2. Safety: Investigator's Responsibilities

All reportable adverse events that occur during this follow-up phase should be fully documented in the research record by the Investigator including the onset date, complete description of the event, severity, duration, action taken, and outcome. The event should be documented on the Adverse Event case report form. The investigator will be responsible for notifying the reviewing Ethics Committee, and if applicable other authorities, of any reportable adverse events according to local regulations.

Adverse events which are possibly, probably, or definitely related to the device must be reported promptly to the sponsor. Adverse events which are unanticipated (UADE) must be reported to the sponsor by telephone or by email as soon as possible, and the completed adverse event CRF must be faxed to the Sponsor within 10 working days of gaining knowledge of the event together with a cover letter describing the event and detailing the medical history.

The investigator shall also supply a copy of the completed adverse event investigation form, together with a cover letter describing the event and detailing the medical history to the Ethics Committee. The investigator will also provide any relevant follow-up information and the outcome of the event as soon as possible.

8.3. Safety reporting: Sponsor's Responsibilities

Sponsor will provide progress reports on safety events to the Investigator to report to the EC as required. The Sponsor will also determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

9. STATISTICAL PROCEDURES

9.1. General considerations

General summary statistics for numeric data will include the available records (n), the mean, the standard deviation (SD), the median, the minimum, and the maximum value. For categorical data, the count and percent of data will be presented with the percent based on the number of subjects with data. Implant survivorship will be measured from time of surgery to time of the first instance of removal of any device component for any reason. Subjects who do not experience a removal for any reason will be censored at the date of last data collection. Kaplan-Meier (KM) estimates will be provided by time point (life tables) and graphically (survival curves).

The Statistic Analysis Plan is found in Appendix III.

9.2. Sample size

The DOD cohort of the PMA consisted of 137 DOD subjects. The sample size is fixed, based on the number of subjects enrolled in the European Cohort Study. Of the 137 DOD subjects included in the PMA Cohort, one died and one was revised by the 3-year follow-up interval. Thus, a total of 135 subjects are eligible for this PAS study and all attempts will be made to continue follow-up on all subjects throughout 10 years, including telephone follow-up for determination of device survival or revision status in cases where subjects fail to return for follow-up visits.

10. ETHICAL CONSIDERATIONS

10.1. Ethical Approval

All participating sites have written EC approval to conduct the European Post-market study at their sites.

10.2. Protocol Amendments

Neither the Investigator nor the Sponsor will modify this protocol without mutual agreement. After agreement to initiate the modification - in the form of a protocol amendment - the Investigator agrees not to implement this modification until instructed to do so by the Sponsor. It will be necessary to obtain FDA and EC approval prior to implementation of any change in the protocol that may affect the scientific soundness or the rights, safety, or welfare of the subjects involved. Notification shall be submitted to the EC of the study site by the Investigator.

10.3. Informed Consent

All study subjects have already signed an EC approved ICF according to 2011:ISO14155 guidelines, GCP guidelines and all applicable national regulations. No additional consenting is required.

10.4. Risk – Benefit Analysis

A. Study Related Risks

Possible risks that may occur as a result of long term follow-up study participation are:

- Subjects will be asked to return to their doctor for follow-up visits at 5, 7 and 10 years and undergo an evaluation to assess their pain and function; however, these are not interventional procedures and are not expected to add significant time to any appointments.
- This study involves the use of x-ray evaluation. X-ray exposure is cumulative over a lifetime and total exposure should be kept to a minimum. However, if the x-ray exposure when participating in the study is equivalent to the exposure the subject would receive if they chose not to participate in the study, there is no additional risk associated with this study.
- As a result of participating in the study there could be a risk of loss of protected subject information confidentiality. All applicable confidentiality standards and data protection and privacy laws will be followed by the Sponsor to ensure that data collected is handled in confidence. Data will be coded and handled only by appropriately qualified and authorized personnel.

B. Study Related Benefits

Because the surgery and all the follow-up visits are the same as when the subject would not participate in this study, there are no additional medical benefits associated by participating in this study. The information gained from this study may help improve the treatment of people that need to undergo total hip replacement.

11. MONITORING PROCEDURES

11.1. Source Documentation

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject (source documents). Examples of source documents are: hospital records, clinic and office charts, x-rays, and research subject files.

11.2. Direct Access

This study may be monitored by the Sponsor or a qualified person designated by the Sponsor. This qualified person could be an employee of the Sponsor or of a contract research organization (Sponsor's agent).

The investigator will provide Sponsor, Sponsor's agents, EC and regulatory agencies with direct access to all source data/documents to permit study-related monitoring, audits, EC review, and regulatory inspections.

11.3. Interim Monitoring Visits

A clinical monitor, whether an employee of the Sponsor or its designee, has the obligation to follow this study closely. In doing so, the monitor will, in addition to maintaining necessary contact with the study site, visit the study sites at periodic intervals according to a schedule determined by the Sponsor.

11.4. Sponsor Audits and Regulatory Inspection

Quality assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format.

11.5. Closeout Visit

A study close out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries, and review regulatory requirements regarding records retention and EC reporting requirements.

11.6. Documentation of Monitoring Visits

Activities associated with a monitoring visit will be documented by the monitor.

11.7. Data Handling and Record Keeping Requirements

Case report forms (CRFs) have been supplied by the Sponsor. Subjects will be identified by a study number and subject identification code. Only the Investigator site will have the key to identify individual subjects.

The Investigator is responsible for the timely and accurate completion of CRFs. All documents related to the study must be securely archived at the study site or in a central archive.

Data required according to this protocol are to be recorded on the case report forms (CRFs) at the time of the scheduled visits. Once a subject is enrolled, completed CRFs should be sent to the Sponsor, either by fax or by e-mail, as soon as possible, and no later than 10 working days upon completion of the CRFs.

11.8. Data Recording and Record Retention

Clinical research records shall be stored in a manner that ensures privacy, confidentiality, security and accessibility of the records both during and after the conduct of the study. The Investigator/Institution will take measures to prevent accidental or premature destruction of those documents. The investigator must retain essential study documents for at least 2 years after the latest of the following: the date the study is terminated or completed or the date the documents are no longer needed to support a premarket approval application. If the Investigator needs to dispose of the documents, the Sponsor should be contacted for approval prior to disposal or destruction. The investigator will retain these documents for a longer period if required by the applicable local laws. If the responsible investigator retires, relocates, or withdraws from responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

12. DEVIATIONS FROM PROTOCOL

A protocol deviation is an instance of failure, intentionally or unintentionally, to follow the requirements of the protocol. Protocol deviations include but are not limited to: endpoint variable criteria, study visits outside the window or missed.

12.1. Protocol Deviation Reporting Requirements

Deviations must be reported to the Sponsor as soon as reasonably possible. When protocol deviations affect the scientific soundness of the study, or the rights, safety or welfare of the study subjects, the Investigator must also report protocol deviations to the EC of the study site.

Investigators and all study staff (staff at site and at Sponsor) are responsible for ensuring adherence to study protocol. During the monitoring visits, the Sponsor representative will review all deviations with the Investigator. If a deviation is discovered outside of a monitoring visit, it should be evaluated via phone, email or letter. Appropriate measures to address the occurrence, additional monitoring visits, or audit of the study should be taken, which may include defining and implementing a Corrective and Preventive Action (CAPA).

13. Reports

Annual reports will be prepared and submitted to the ECs in accordance with on-going approval requirements.

It is expected that it will take 7 more years to complete data collection for all subjects at the 10-year follow-up interval. Once all of the study data is collected and the database is closed for analysis, it is anticipated that the data analysis and the preparation of a final PAS study report will take three (3) months to complete.

The sponsor will submit reports to the US FDA every 6 months for the first two years of the study, and then annually to completion.

14. Publication policy

14.1. Multicenter Publication

The sponsor may invite the investigator to participate in a multicenter publication of the study results, in which case it will be ensured that the documents submitted for publication comply with the publisher's requirements for authors and contributors. If the publisher has no such requirements, it will be ensured that the publication meets the authorship and contributorship requirements as stated in the current Smith & Nephew Global Policy and Procedure relating Scientific Disclosures. Also, the sponsor will select a publisher based on mutual agreement with the investigators, who are invited to participate in the publication.

14.2. Investigator Publication

The investigator may publish his/her own data subject to the following restrictions:

- the multicenter manuscript must be published prior to investigators publishing their own data;
- the manuscript shall be submitted to the Sponsor for review prior to submitting the manuscript for publication;
- the manuscript must reference the study multicenter manuscript.

14.3. Authorship

The sponsor may invite the investigator to participate in a multicenter publication of the study results. The sponsor will select a publisher based on mutual agreement with the investigators who are invited to participate in the publication. Unless otherwise required by the journal of publication or the forum in which a presentation is made, authorship will comply with ICMJE current Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. ICMJE recommends that authorship be based on the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and
- Drafting the work or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

Subject to a publisher's copyright, Site and/or Investigator will own the copyright on publications and other copyrightable material produced as a result of the Study.