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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

Table of Contents

1. Study Contact Information

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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.

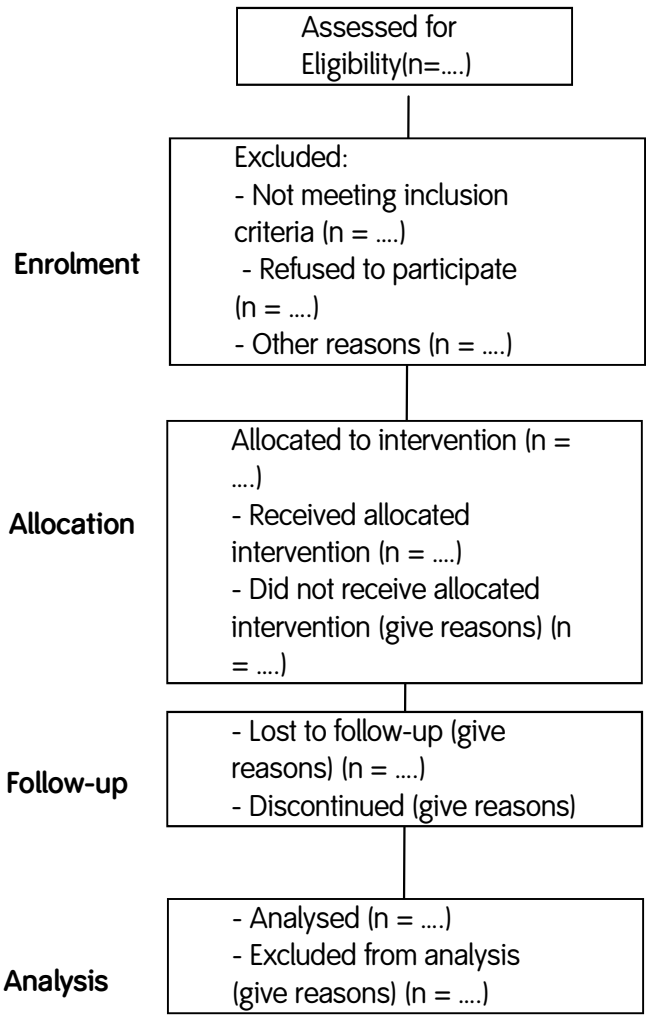

Figure 1

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.

Appendix I

Smith & Nephew R3 Acetabular Hip Study
Image Evaluation Protocol

Purpose

The purpose of the Image Evaluation Protocol (IEP) is to provide instructions to the independent radiologist for evaluation of the images in the Smith & Nephew R3 Acetabular Hip system study. The IEP is intended to be a reference guide to ensure that all images across patients and longitudinally are being evaluated in a consistent manner.

Study Summary

Total hip arthroplasty (THA) is the gold standard treatment of severe hip osteoarthritis. 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.

Smith and Nephew (S&N) is performing a multicenter prospective observational post-market clinical follow-up study that will include up to 500 patients who will have total hip replacement with the R3 Acetabular System and either cemented or cementless hip stem. The objective of this study is to determine the long-term safety and effectiveness of the R3 Acetabular System. The central hypothesis is that implant survivorship 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 per Kaplan Meier analysis.

Device Components

The R3 system was designed to provide the ability to tailor the implant to the individual patient requirements. 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 called Stiktite. This coating contains sintered asymmetric titanium grains, which allows for an enhanced scratch fit and stability.

The hip system used in this study consists of R3 acetabular cups and three liner options: metal (CoCr and Oxinium), ceramic (BIOLOXforte and BIOLOXdelta) and XLPE. The modular femoral heads mate with existing, commercially-available Smith & Nephew Orthopaedics uncemented or cemented femoral stems.

Goal of Radiographic Analysis

One of the safety measures in this study is the radiographic analysis of the operated hip over time. This includes surgery- and device-related events such as device revision, component failure, malfunction, migration or loosening that can be assessed by radiograph. 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.

Smith & Nephew R3 Acetabular Hip Study
Image Evaluation Protocol

Imaging Time Points

AP and lateral radiographs will be obtained before discharge in addition to at 1 year, 3 years, 5 years, 7 years and 10 years postoperatively. Additionally, the 1-year follow-up radiograph set includes a full pelvic overview (including at least 20 cm of the proximal femur).

In this statement of work (SOW) between S&N and ImageIQ, a subset of the total patient cohort will be analyzed at the discharge, year 1, year 3, and year 5 time points. Some patients in this R3 study have been previously analyzed in a prior SOW. At the conclusion of this SOW, all patients in the R3 study will have been analyzed at the discharge, year 1, year 3 and year 5 time points. A new SOW will be contracted to cover the analysis of the 7- and 10-year time points.

In addition to the time points above, a subject may have additional imaging performed according to the specifications in the study Protocol or at the investigator's discretion.

Workflow

Please refer to Appendix A: Imaging Workflow for a diagrammatic depiction of the workflow.

Reader Approval and Training Overview:

- Images will be read by 1 central independent radiologist.
    - The reader will be approved by Smith & Nephew and ImageIQ prior to participation in the study, as documented in D-F465-003 Radiologist Approval Form.
    - Radiologist shall agree to the guidelines for image analysis and workflow put forth in this document. Agreement will be documented by signing the D-F465-007 Independent Radiologist Agreement.
    - Radiologists will complete project specific training and the D-F465-008 Radiologist Training form will be completed upon conclusion of the training.

Image Workflow Overview:

- Images will be transferred by S&N to ImageIQ via secure FTP
- Image sets will undergo Quality Assessment (QA) weekly and CRF completion in monthly batches after the images are received via FTP.
- Quality Assessment
    - Quality check will include that proper de-identification of the images was performed, that a complete image set for the patient time point was received, and that the image quality is sufficient for measurements to be completed.
    - Detailed instructions for quality assessment are contained in the D-F465-004 Image QA Guidelines document.
    - Images that fail QA will still be assessed by the reader
        - All fields that can be assessed in the CRF should be completed.
        - Fields that cannot be assessed will be marked as "Not Evaluable"

Smith & Nephew R3 Acetabular Hip Study
Image Evaluation Protocol

Case Report Form Completion Instructions

- As the images are reviewed and measurements assessed, each field of the CRF shall be completed.
- For each follow-up (post discharge) assessment, reader must view discharge scans with corresponding follow-up scan to ensure landmarks are consistently selected for measurements
- If image quality is insufficient to enable assessments of one or more metrics, “Not Available” (NA) will be written in for those fields that cannot be assessed.
    - Standardized language for the reasons when a field is “NA” are listed below
        - Required/necessary images missing
        - Images under/over exposed
        - Some structure are outside of the field of view (FOV)
        - Patient positioning or radiograph view are incorrect
- Each field must be completed before finalization on the CRF.
- Once complete, the CRF shall be signed, dated, and sent to ImageIQ.

Image Evaluation and Measurement Instruction

The following instructions and techniques will be used in evaluation of the radiographs for each patient in the study. The patient identifier, time point, and date of acquisition will be present in the image DICOM headers and recorded in the CRF. The CRFs in this study are time point specific. There is a different bar coded CRF for discharge, year 1, year 3, year 5, year 7, and year 10. Always select the CRF for the appropriate time point to complete.

Since many images in this study are retrospective and acquired by different sites using variable acquisition techniques, the variability in acquisition and image quality is unknown. The type of views sent to ImageIQ and used for analysis will be recorded for each patient time point. There may be variation in some of the measurements due to the variability in acquisition across patients and longitudinally within a patient’s set of images.

The femoral head implant diameter will be measured and recorded for scale factor conversion. The femoral head diameter has a known value for each patient and thus can be used reliably for conversion. The scale factor conversion will be completed before images are sent to the radiologist for review. The process for conversion and justification of the need for conversion of the scale factor are detailed in Appendix B.

Units will be displayed on the CRF fields. All length measurements will be in whole mm and all angle measurements will be in whole degrees unless otherwise stated in the CRF and IEP.

The following instructions pertaining to image use and substitution apply to this study:

- Every follow up time point scan will be compared to the discharge time point. For each follow-up, post discharge, reader must view discharge scans with corresponding follow-up scan to ensure landmarks are consistently selected for measurements
- If more than one copy of a particular AP or lateral scan is available, the independent radiologist will select the best quality scan for assessment
- If the radiographs are missing or have poor quality such that a reasonable assessment cannot be made, a substitute radiograph acquired immediately before or after the particular time point (+/- 6 months) may be used if available. If not, the scan/time point will be treated as unavailable.

- If an AP or lateral view film is available but has a portion that is of poor quality or under/over-exposed such that a reasonable assessment is not possible, then the obscured AP or lateral radiographic zone affected will be left blank or marked as “NA” in or next to the appropriate corresponding fields on the case report form.
- Lauenstein radiographs may be used when lateral radiographs are not obtained or available.
- AP hip may be used at Year 1 as a substitute for AP pelvis when the AP pelvis was is obtained or unavailable in order to ensure partial information is collected
- AP pelvis may be used at all time points as a substitute for AP hip when the AP hip is not obtained or is unavailable.

Discharge Time Point: Independent Review Immediate Postoperative CRF

At the discharge (immediate postoperative) time point, AP hip and lateral images will be used to assess cup position and femoral stem position. The CRF fields are shown below.

Cup position:

- Cup position at discharge will be estimated using lateral inclination.
- The location of the contralateral ischial tuberosity will be estimated and the transischial tuberosity line drawn.
- Orientation of the acetabular cup will be assessed by measuring the angle formed by a line along the lateral margin of the acetabular component intersecting the estimated transischial tuberosity line (**Figure 5**, "Inc"). The inclination angle of the acetabular cup is determined by drawing a tangential line to the face of the prosthesis and a second line drawn through the roentogenographic teardrop landmarks.
- Using a digital tool, measurement of the subtended angle of the two lines determines the amount of inclination of the prosthesis.
- Normal acetabular inclination is between 30 and 50 degrees
- Acetabular inclination at each follow up time point will be compared to the discharge time point

Femoral Stem Orientation:

- Orientation at each follow up time point will be compared to the discharge time point.
- Orientation will be classified as neutral, varus or valgus.
- Assessment will be made by measuring the angle between the lateral surface of the shaft of the femur and the longitudinal axis of the femoral component through the center of the medullary canal.
- If varus or valgus, the measured angle will be recorded in whole degrees on the CRF, otherwise neutral will be marked

Year 1 Time Point: Independent Review Implant Position

This page of the CRF assesses the implant positioning at the Year 1 follow up time point. Inclination, anteversion, femoral stem position, and leg length discrepancy are assessed. The femoral stem orientation will be assessed as described above (same as the discharge time point). Instructions for the inclination, anteversion, and leg length discrepancy are described below.

Cup position

☐☐☐ ° Inclination

☐☐☐ ° (+) = anteversion
(-) = retroversion

Stem position

☐☐☐ ° (+) = valgus
(-) = varus

Leg Length Discrepancy: *(Tick one box only)*

☐ None
☐ Ipsilateral longer → ☐.☐ cm
☐ Ipsilateral shorter → ☐.☐ cm

***Acetabular Inclination*:**

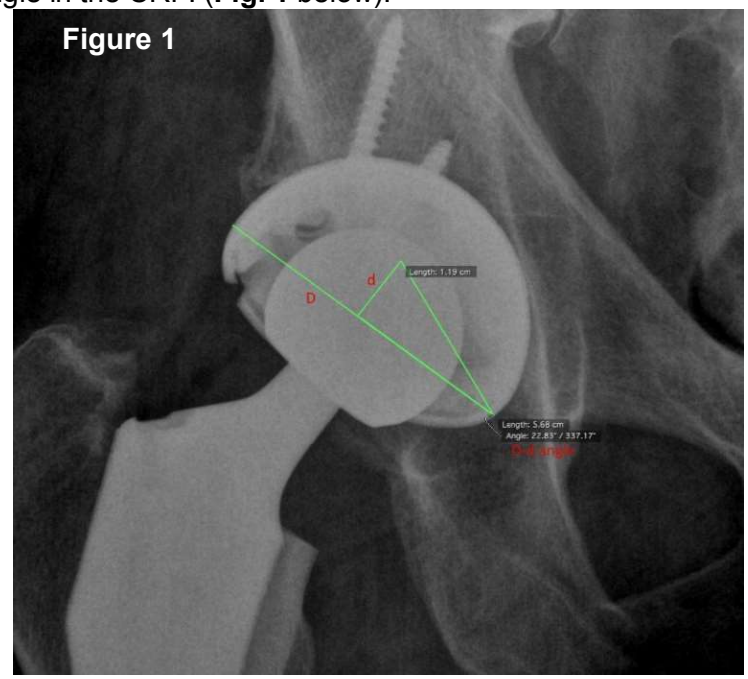
- The AP pelvis view will be used to evaluate acetabular inclination.
- Corresponding discharge scans must be viewed in conjunction with 1 year radiographs to ensure consistency in landmark selection
- Orientation of the acetabular cup will be assessed by measuring the angle formed by a line along the lateral margin of the acetabular component intersecting the bi-ischial line (**Figure 5**, "Inc"). The inclination angle of the acetabular cup is determined by drawing a tangential line to the face of the prosthesis and a second line drawn through the roentogenographic teardrop landmarks.
- Using a digital tool, measurement of the subtended angle of the two lines determines the amount of inclination of the prosthesis.
- Normal acetabular inclination is between 30 and 50 degrees
- Differences in acetabular inclination less than 4 degrees are not considered significant.

Acetabular Cup Anteversion:

- Excessive anteversion of the acetabular cup is currently believed to be associated with undesirable events such as decreased head coverage, posterior impingement, and increased metal debris/wear.[1] Conversely, inadequate anteversion is associated with increased risk for bearing surface wear or psoas tendonitis which could result from the lack of bony coverage of the anterior lip of the cup
- Corresponding views of discharge scans must be evaluated in conjunction with 1 year radiographs to ensure consistency in landmark selection
- A line D is drawn between the furthest distances around the acetabular rim. A perpendicular line, d,

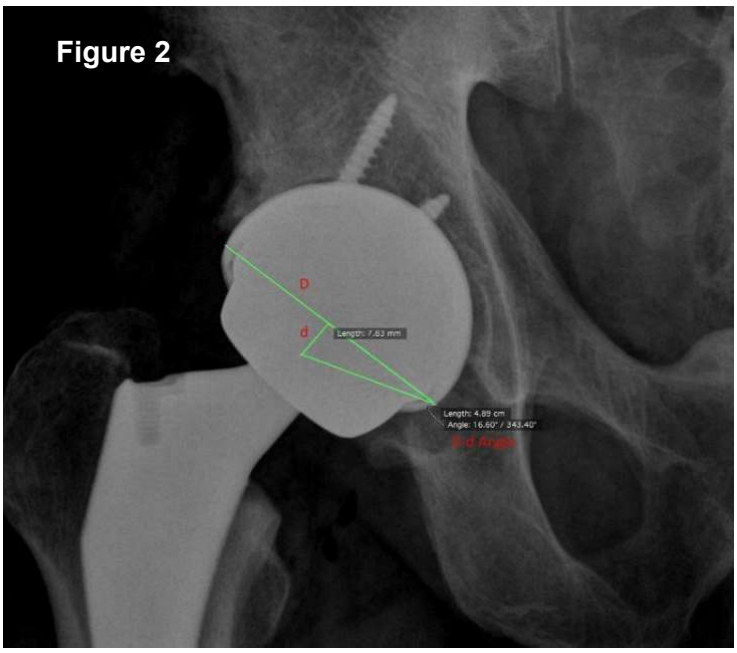
is drawn from the center of D to the nearest equitorial rim. The D-d angle is drawn and corresponds to the anteversion angle in the CRF. (**Fig. 1** below).

Figure 1



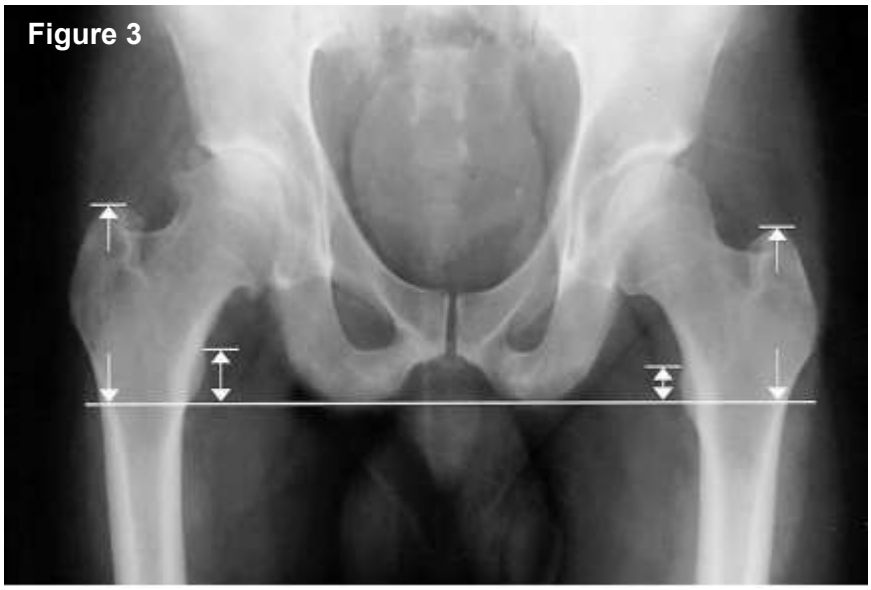
- Some femoral head components are radiodense, and the equatorial rim cannot be directly seen and must be inferred. In such a case, line D is drawn between the furthest distances around the acetabular rim. A perpendicular line, d, is drawn from the center of D to the nearest "inferred" equitorial rim. The D-d angle is drawn and corresponds to the anteversion angle in the CRF. (**Fig. 2** below).

Figure 2



Leg length discrepancy (LLD):

- Leg length discrepancy will be measured using the AP pelvis image (**Fig 3** below[3]).
- A line is drawn through the bottom of the ischial tuberosities. On each side, the distance from the superior aspect of the lesser trochanter landmark to the line is measured. The difference between the two is the radiographic leg-length discrepancy. The tip of the greater trochanter may be used as an alternative.[3] Using fixed points on the pelvis will minimize the bias encountered in LLD measurements. A leg length discrepancy of >10 mm is considered significant.



Independent Review X-Ray Follow Up – Years 1, 3, 5, 7 and 10 (Page 1)

The independent review X-ray follow up CRF is a 2 page CRF that is completed at every follow up time point (Years 1, 3, 5, 7 and 10). The first page assesses component positioning and movement, as well as heterotopic ossification and component fixation.

Subsidence and Migration:

Cup position

- ☐ unchanged
- ☐ migration cranial ☐☐ mm
- ☐ migration medial ☐☐ mm
- ☐ change in inclination ☐☐ °

Stem position

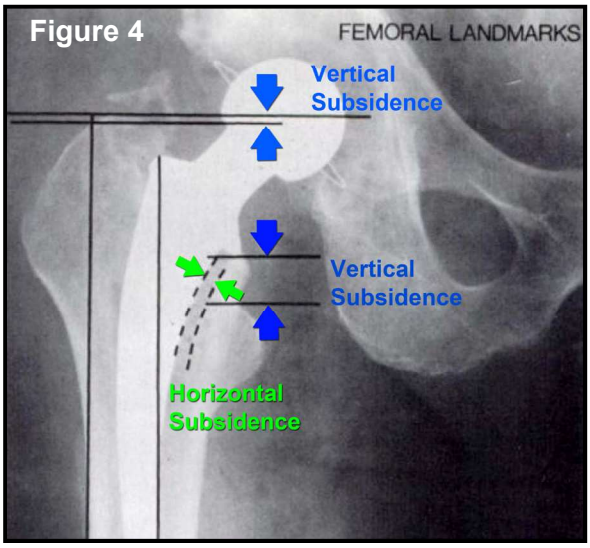
- ☐ unchanged
- ☐ varus tilted ☐☐ °
- ☐ valgus tilted ☐☐ °
- ☐ subsidence ☐☐ mm

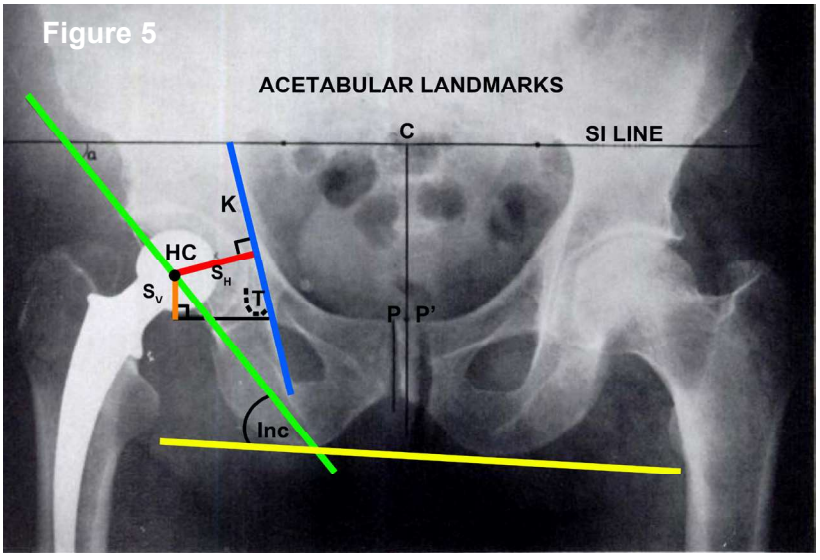
Smith & Nephew R3 Acetabular Hip Study
Image Evaluation Protocol

Noticeable settling or sinking of a prosthesis component into the bone following total joint implantation is known as subsidence or migration and may result in loosening and eventual failure of the implant. The amount of subsidence may vary in severity from subtle changes of the bone to actual movement of the device from the original fixation position. A discernable shift or migration can occur in either the acetabular component or the femoral component. Implant positions relative to various landmarks on both the baseline post-operative and post-operative radiographs will be used to determine subsidence according to the methods described by Sutherland, Wilde, Borden, & Marks.[4]

Using standardized reference points (see **Figure 4** below), migration of the acetabular cup and femoral component will be reported in whole millimeter increments. Standard rounding rules will be used to round the nearest millimeter.

Comparison measurements of the prosthesis are sensitive to patient position, x-ray techniques, and image magnifications.[4] Due to the inherent variability in radiographic measurements, only changes ≥ 5 mm are to be considered to be significant and evidence of migration or subsidence. All measurements will be reported as a change with respect to discharge cup and stem locations. Thus, to ensure consistency in landmark selection discharge scans must be evaluated simultaneously with each follow up time point.





Acetabular Inclination measurement:

- The AP pelvis view will be used to evaluate acetabular inclination/tilt.
- Acetabular angular motion will be reported as a change in acetabular cup inclination with respect to discharge cup inclination, thus corresponding discharge scans must be viewed in conjunction with the current time point
- Inclination of the acetabular cup will be assessed as described above by measuring the angle formed by a line along the lateral margin of the acetabular component intersecting the bi-ischial line (**Figure 5**, "Inc"). The inclination angle of the acetabular cup is determined by drawing a tangential line to the face of the prosthesis and a second line drawn through the roentogenographic teardrop landmarks.
- Using a digital tool, measurement of the subtended angle of the two lines determines the amount of inclination of the prosthesis.
- Normal acetabular inclination is between 30 and 50 degrees
- Differences in acetabular inclination less than 4 degrees are not considered significant.

Femoral Stem Position measurement:

- Orientation at each follow up time point will be reported as a change with respect to the discharge timepoint; corresponding discharge radiographs must be viewed simultaneously with each follow up time point
- Orientation will be classified as neutral, varus or valgus.
- Assessment will be made by measuring the angle between the lateral surface of the shaft of the femur and the longitudinal axis of the femoral component through the center of the medullary canal.
- If varus or valgus, the measured angle will be recorded in whole degrees on the CRF.

Femoral Subsidence measurement:

- Changes along the vertical axis will be determined by referencing the superior tip of the greater trochanter to the center of the femoral head and the vertical distance from the most inferior margin of the shoulder of the femoral component to the most proximal point on the lesser trochanter.[4] See **Figure 4** for femoral landmarks.
- Measurements will be reported as a change with respect to discharge stem location thus corresponding discharge radiographs must be viewed simultaneously with each follow up time point.

Acetabular Cup Subsidence measurement:

- Acetabular migration assessment will be performed on the AP pelvic image (**Fig 5** above).
- Acetabular cup migration (subsidence) will be reported as a change in the measured distance along the vertical or horizontal axis in relationship to the hip center (HC) of the acetabular component
- The center of the acetabular component will be used as a standard reference point. The Kohler (K, blue) line, drawn from the pelvis along the medial aspect of the ilium and ischium will be used as a landmark in relation to the HC to determine movement along the horizontal axis (SH, red line).
- Vertical movement (SV, orange line) will be the shortest distance between the HC and a horizontal line from the inferior aspect of the teardrop (T).
- As with the femoral subsidence described above, it is difficult to eliminate all errors from positioning thus measured changes in relationship to referenced landmarks less than 5 mm are not considered significant for acetabular cup migration.[4]
- Measurements will be reported as a change with respect to discharge acetabular cup location thus corresponding discharge radiographs must be viewed simultaneously with each follow up time point

Although the AP pelvic image is preferred for determining migration, if the image is not available or is of poor quality, the AP hip view may be used to determine cup migration. In the AP hip image, a reference to the horizontal axis will be used to measure the horizontal distance between the midpoint of the lateral edge of the metal shell and a line drawn through the center of the teardrop. Movement along the vertical axis will be determined by measuring the distance from the midpoint of the edge of the metal outer shell to a line tangent to the inferior edges of both teardrops on the AP pelvic view.

Stem Fixation:

Stem fixation - uncemented stems (Engh et al)

- ☐ not applicable
- ☐ fixation by bone ingrowth
- ☐ stable fibrous ingrowth
- ☐ unstable implant

Only uncemented stems will be used in this study. There are three options for stem fixation assessment: fixation by bone ingrowth, stable by bone ingrowth, and unstable implant. Further definition of each of these terms follows:

- Fixation by bone ingrowth
  - Spot welding (new bone formation contacting the prosthesis) and absence of lucent lines next to porous coating
- Stable fibrous ingrowth:
  - Unchanged radiolucent lines at bone-metal interface measuring <2 mm in width, often associated with a sclerotic line
- Unstable implant
  - Progressive increase in radiolucent lines at the bone-metal interface, component migration, or pedestal formation (bony hypertrophy around tip due to stress loading)

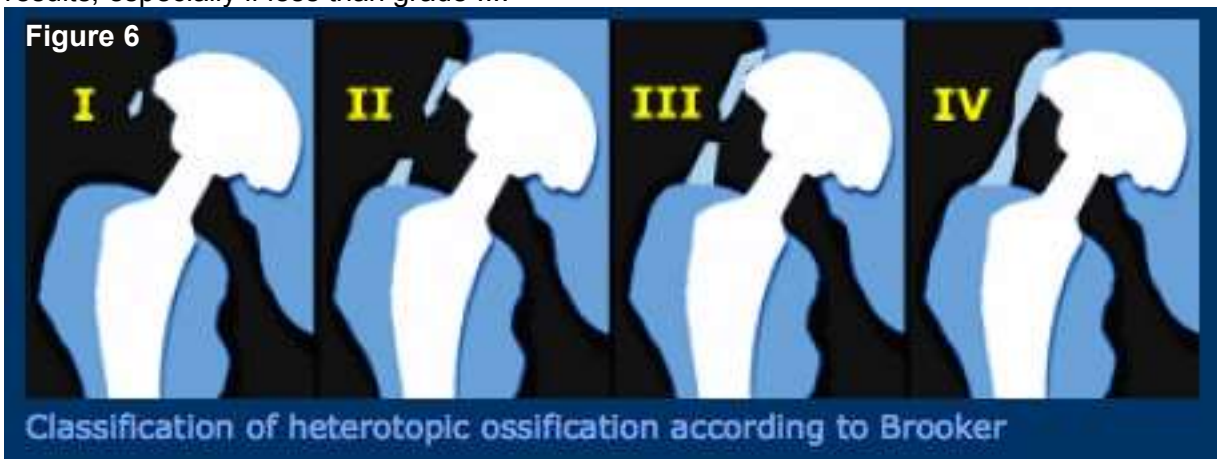
Heterotopic Ossification:

Heterotopic ossification (Brooker Classification) *(Tick one box only)*

- ☐ Grade 0 none, no islands of bone
- ☐ Grade I islands of bone within the soft tissues about the hip
- ☐ Grade II bone spurs from the pelvis or proximal end of the femur leaving at least 1 cm between opposing bone surfaces
- ☐ Grade III bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm
- ☐ Grade IV apparent bone ankylosis of the hip

The formation of ectopic bone is a complication that occurs with a moderate percentage of patients following total hip replacement. AP hip and lateral radiographs will be reviewed for the formation of heterotopic ossification and if present will be graded according to the Brooker Classification. The Brooker classification uses a scale consisting of four levels.[6] See **Figure 6** for illustration[7]. The amount of heterotopic bone formation will be graded according to the amount of ectopic bone demonstrated on the radiograph, although it is noted that heterotopic ossification classifications are not always associated with reduced postoperative functional results, especially if less than grade III.[6]

Figure 6



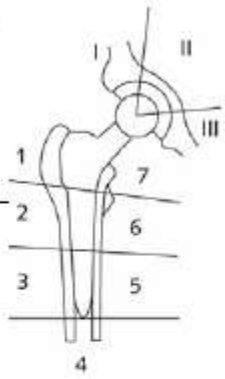
Smith & Nephew R3 Acetabular Hip Study
Image Evaluation Protocol

Independent Review X-ray Follow up – Years 1, 3, 5, 7 and 10 (Page 2)

On this page of the CRF, radiolucencies, osteolysis, atrophy, and hypertrophy will be assessed in the acetabular and femoral regions. All assessments should involve a comparative evaluation with all pre-existing longitudinal radiographs for a given subject. If no findings are discovered, check “no” in each section and the form is complete.

Otherwise, select “yes” in each section affected by radiolucencies, osteolysis, atrophy, and/or hypertrophy and complete the rest of the form.

	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone I	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone II	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone III	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone IV	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone V	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone VI	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	minimal 1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone 1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
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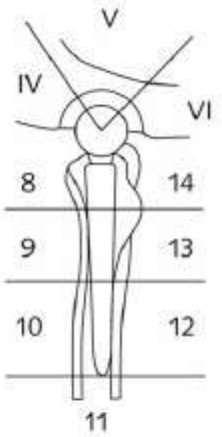
Zone 8	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 9	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 10	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 11	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 12	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 13	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 14	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



Delineation of Zones:

To differentiate radiographic findings in the femoral stem area, the stem will be divided into numbered zones as described by Gruen, McNeice, and Amstutz (1979)[8]. Zones are illusatrated in the CRF figure above.

- The bone-prosthesis interface of the femoral component in the AP orientation will be divided into 7 zones.
- Corresponding areas in the lateral view of the femoral component will also be divided into seven zones numbered 8-14 to differentiate the specific area and view in which it was noted.
- The acetabular region in the AP projection only will be divided into three zones as described by DeLee and Charnley (1976).[9]

Radiolucencies:

Areas of the bone surrounding the implanted device which show low density lines or rounded areas are considered radiolucencies which may indicate areas of potential concern.[10] While radiolucencies can be found in well fixed, asymptomatic total hip replacements, the chance of loosening increases with the extent and thickness of radiolucent areas at the bone-implant interface. In particular, implants with radiolucent areas which appear as continuous gaps around the implant greater than or equal to 2 mm in width have the highest probability of loosening.[5] Radiolucencies observed in varying shapes indicative of localized bone resorption, cystic erosion, increased shear stress, and diffuse linear forms are normally considered to result from expansion of the periprosthetic cortical bone.[10]

Areas of radiolucency in linear form in the zones around the implanted device will be measured and reported, irrespective of root cause (lesions, resorption, shear stress, etc.). Each zone (Figures in CRF above) will be evaluated for radiolucencies and the maximum width of the radiolucent line measured will be noted in whole mm using standard rounding rules (≥2 mm is considered significant). Any observed radiolucencies will be tracked longitudinally.

Osteolysis:

Osteolysis is the dissolution of bone through the active resorption of native bone matrix by osteoclasts as a result of disease, infection, or ischemia. The development of periprosthetic osteolysis is not an uncommon occurrence following joint replacement and is believed to be a secondary response of macrophage activity stimulated by microscopic wear particles released from articulation of components in an artificial hip joint.[11] The resulting biological cascade promotes progressive bone degeneration leading to implant loosening or fracture. While originally associated with cemented components, periprosthetic osteolysis has also been demonstrated with non-cemented devices of various materials[11] such as ceramics, polyethylene, and metals. In particular components consisting of ultra-high molecular weight polyethylene have shown higher incidence of osteolysis due to increased wear debris.[12] Regardless of the etiology, distinguishable osteolysis or resorption will be documented on the case report form according to the zones in which changes are observed.

All radiographs are to be reviewed for evidence of osteolysis. The presence of osteolytic lesions will be noted on the case report form according to zonal areas involved. The maximum width of the lesion will be noted in whole mm using standard rounding rules. Osteolytic lesions may form in localized areas surrounding the implant shaped as linear, cystic, or expansile regions. AP-pelvis, AP-hip and lateral radiographs are to be reviewed for evidence of osteolysis. If an osteolytic lesion is found, subsequent radiographic evaluations should be used to determine whether the lesions are stable or progressive to help characterize prognosis for implant survival (include in the “Notes” section of the CRF).

Atrophy:
Cortical bone thinning (atrophy) is associated with bone loss. Adaptive atrophy commonly occurs with cementless components in the superomedial acetabulum and the proximal medial femur as a result of stress shielding. The extent in millimeters and location of bony atrophy should be recorded using the zonal map.

Hypertrophy:
Cortical hypertrophy often occurs as a result of increased stress loading. The extent in millimeters and location of bony hypertrophy should be recorded using the zonal map.

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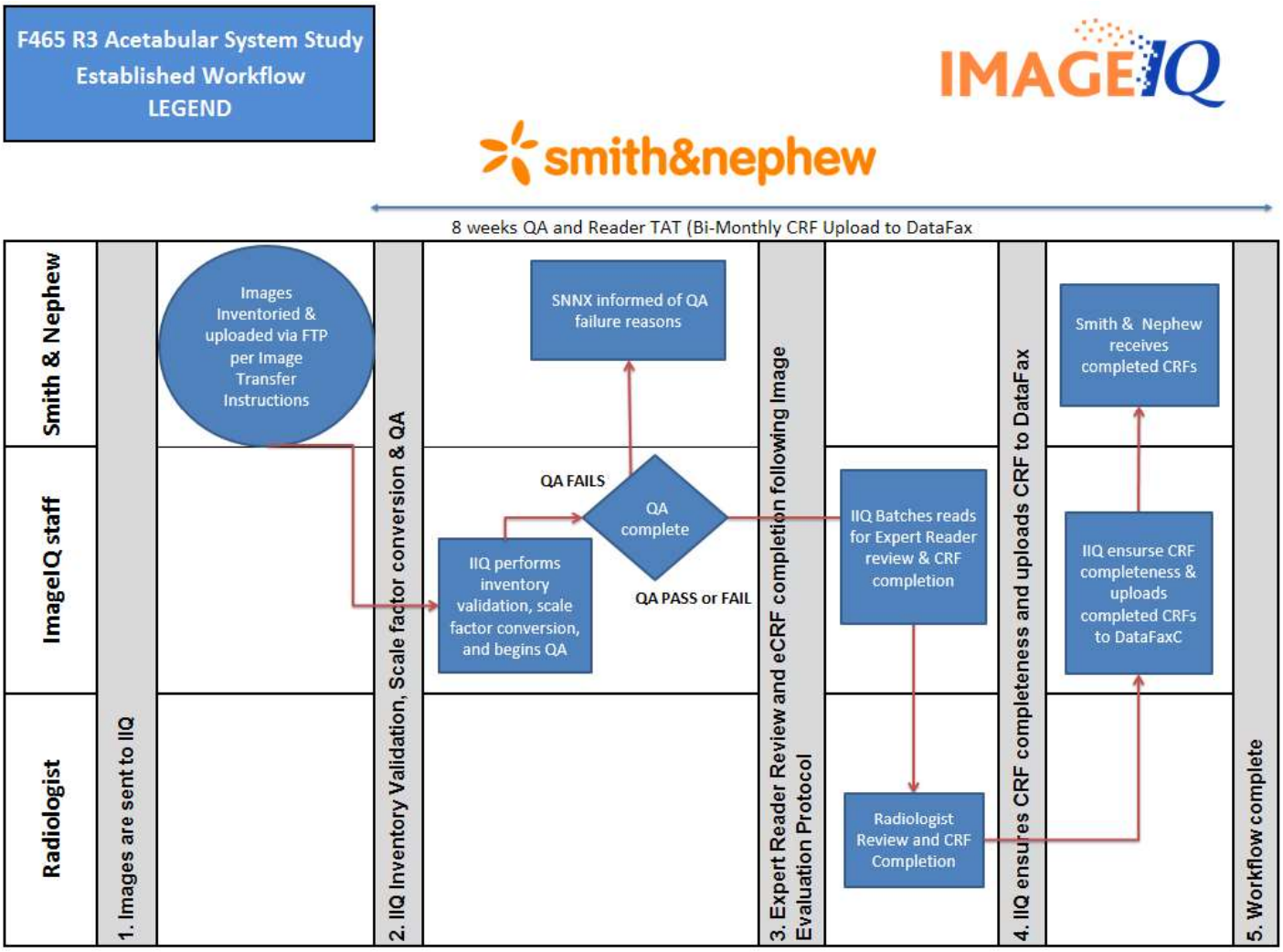
Appendix A: Imaging Workflow



Appendix B: Radiograph Calibration Correction Technique

All images will be presented to the reader in DICOM file format for loading and assessment in an approved DICOM viewer. Images arriving in non-DICOM format (TIFF, JPEG, etc) will be converted to DICOM format following calibration as described in detail below. Regardless of the originating format, all images will be recalibrated using this procedure

All radiographs, discharge, 3 month, year 1, year 2, and year 3, will need to be evaluated for correct calibration factor (CF) (a conversion factor embedded in a DICOM image header that enables conversion between pixels and unit length) to ensure accurate length measurements are reported. This correction is critical since multiple CRF assessments involve quantitative measurements including leg length discrepancy (cm), cup migration (mm), stem subsidence (mm), width of radiolucent lines (mm), atrophy (mm), and hypertrophy (mm).

Illustrating the necessity for recalibration/correction, an example from a previous study (Patient 3050, year 1 time point) is shown below (Figure 1). Figure 1a shows the entire pelvis and 1b is a magnified view of the femoral head of the implant in the pelvic view. Figure 1c shows the original lateral image and 1d is a magnified view of the femoral head of the implant in the lateral view. Lines were drawn measuring the diameter of the femoral head and acetabular cup rim. If the MSF is embedded correctly in the image header, these measurements should match on the AP pelvic and lateral views, as the implants are spherical and no warping is evident in the radiographs.

The diameter of femoral head measured 4.12 cm (41.2 mm) on the AP Pelvis x-ray and 5.54 cm (55.4 mm) on lateral x-ray. These measurements deviate by 29% for the same object in different views as calculated by the equation:

$$Percent\ Difference = \left|\frac{X - Y}{(X + Y)/2}\right| \times 100$$

Similarly, the diameter of acetabular cup was measured as 6.29 cm in AP Pelvis and 8.44 cm in lateral view (also a 29% variation).

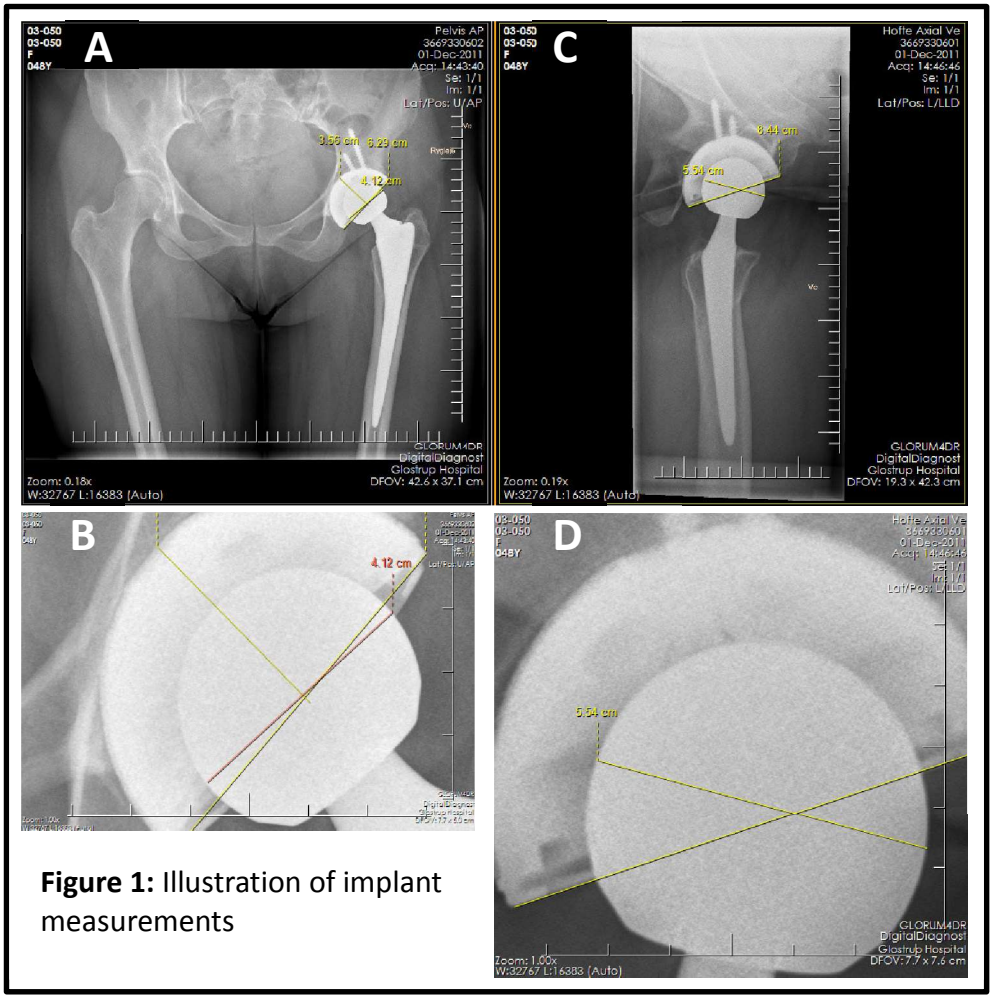


Figure 1: Illustration of implant measurements

Patient 3050 was implanted with an Oxinium head type, size 36. This implant has an outside diameter of 35.9 mm, as reported by S&N. When compared to the known femoral head diameter of 35.9, the AP pelvic measurement has a percent error of 15% and the lateral measurement has a percent error of 54%, as calculated by the following equation:

$$Percent\ Error = \left|\frac{X - Y}{Y}\right| \times 100\ where\ Y\ is\ the\ exact\ (known)\ value$$

As a result of these discrepancies, any quantitative measurements performed on the radiographs using the existing CF, could produce a 15-54% error. For example, a measured radiolucent line of 2.2 mm on the lateral image is actually only 1.12 mm. Since the CRF bins radiolucent lines in buckets of “0 up to 1mm”, “1 up to 2 mm”, and “> 2 mm”, data would have been entered incorrectly (a check in the “> 2 mm” box instead of the correct box of “1 up to 2 mm”).

Smith & Nephew R3 Acetabular Hip Study
Image Evaluation Protocol

To ensure image headers contain an accurate CF, an additional evaluation step will be implemented for all images in this study followed by recalibration if necessary.

Procedure for the Evaluation Step:

Step 1: Each radiograph will be opened (Figure 2). The femoral head of the implant will be magnified (Figure 3) and a best-fit circle will be drawn around the femoral head to determine its diameter in pixels. Three points on the femoral head will be selected in order to create the circle (Figure 4, arrows highlight the 3 points selected).

Step 2: The diameter of the circle in pixels will be calculated and output to a spreadsheet for each image. The image name (containing the patient ID, time point, date of acquisition, and radiographic view) will also be exported with the diameter. In addition, the type of image (DICOM or TIFF) and original embedded scale factor (for DICOM only) will be copied from the headers into the spreadsheet.

Step 3: The actual diameter of the femoral head for each implant, as reported by S&N's product development team, will be reported in the same spreadsheet. The diameter is specific to the implant size and material (Table 1) and is specific to the individual patient.

Step 4: The CF will be calculated by dividing the actual femoral head diameter (in mm) by the diameter of the head (in pixels) measured in Step 1. The resulting number is the CF in units of mm/pixel. This number will allow conversion between pixels and mm for any measurement on a given image. Figure 5 is a snapshot of the spreadsheet layout.

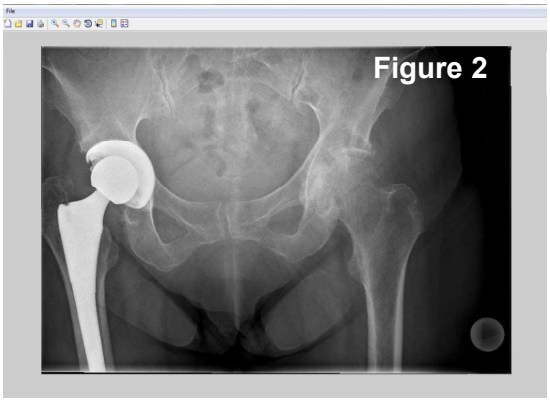


Figure 2

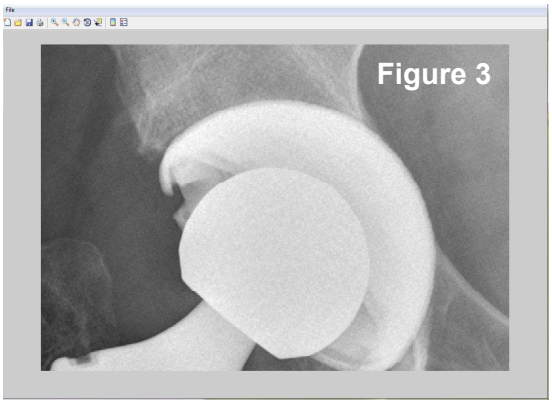


Figure 3

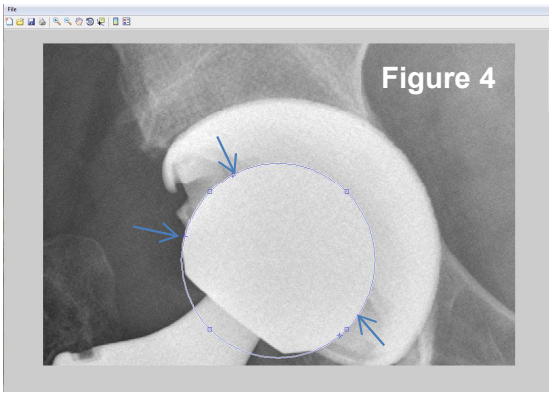


Figure 4

Table 1: Femoral Head Diameters

Figure 5	Size	Outside Diameter (mm)
OXINIUM	28	27.9
	32	31.9
	36	35.9
	40	39.9
	44	43.9
CoCr	22	22.2
	26	25.9
	28	27.9
	32	31.9
	36	35.9
	40	39.9
	44	43.9
Biolox Forte	28	28.0
	32	32.0
	36	36.0
Biolox delta	28	28.0
	32	32.0
	36	36.0

Image Name	File Type	Reported Pixel Spacing (mm)	Known Length (mm)	Measured Length (pixels)	Actual Pixel Spacing (mm)
2042 1y ap 20111006	DICOM	0.143	32.00	273.22	0.11712
2042 1y lat 20111006	DICOM	0.1	32.00	395.25	0.08096
2043 1y ap 20111017	DICOM	0.143	36.00	319.19	0.11279
2043 1y lat 20111017	DICOM	0.143	36.00	300.03	0.11999
2045 1y ap 20111018	DICOM	0.143	32.00	275.42	0.11619
2045 1y lat 20111018	DICOM	0.1	32.00	405.91	0.07883
2046 1y ap 20111025	DICOM	0.143	36.00	295.13	0.12198
2046 1y lat 20111025	DICOM	0.1	36.00	427.09	0.08429
3001 1y ap 20100823	DICOM	0.139425	35.90	313.93	0.11436
3001 3y lat 20120709	DICOM	0.139	35.90	408.55	0.08787
3001 3y pelvic 20120709	DICOM	0.139	35.90	326.04	0.11011
3002 1y ap 20100823	DICOM	0.14126175	35.90	302.82	0.11855
3002 1y lat 20120116	DICOM	0.14443	35.90	379.36	0.09463
3002 3Y pelvic 20120827	DICOM	0.131	35.90	311.43	0.11528
3003 1y ap 20100906	DICOM	0.143	35.90	309.23	0.11609

Figure 5: Spreadsheet Output

If the measured CF matches that of the CF embedded in the DICOM image, then the X-ray "passes" evaluation and will be securely transmitted to the radiologist for CRF completion.

If the measured CF does *not* match that embedded in the DICOM image, then the X-ray "fails" calibration and will be moved into the correction step. The corrected CF will be different for every "failed" image so each X-ray will be evaluated and re-calibrated individually.

Procedure for the Re-calibration Step:

Images requiring CF correction will be moved into a separate folder. The new corrected CF will then be embedded in the DICOM header in the place of the old (incorrect) CF. The file name will be automatically appended with "recalibrated" at the end of the existing file name to distinguish it from the original file. The "recalibrated" image will contain a CF that will enable accurate length measurements of any feature of interest (the implant head, radiolucencies, migration, etc…).

The DICOM headers in recalibrated images will also contain the patient ID and time point information in specific tags. Many sites may strip out patient information (de-identify) but not include patient ID and timepoint information in consistent tag locations and in specific formats so a check is performed to ensure that each image contains the patient ID in the appropriate format and tag within the DICOM header. Images for each patient through all time points will be organized into individual patient folders and transmitted securely to the radiologist for completion of the CRF.

Appendix II

DataFax #107 Plate #060 Visit #260

smith&nephew	Clinical Follow-up (page 1 of 2)	Project No: R3 Study Patient No:

5 Years

Date of Assessment: Day Month Year

Clinical follow-up done

☐ yes ☐ no

General Findings

Complications since last visit

☐ no

☐ yes
*Please complete **adverse event** form*

Charnley Classification
(Tick one box only)

☐ A only ipsilateral hip involved

☐ B both hips involved

☐ C other factors affecting locomotion

Patients Opinion

Satisfaction of patient *(Tick one box only)*

☐ very satisfied

☐ satisfied

☐ partly satisfied, partly dissatisfied

☐ dissatisfied

☐ very dissatisfied

Radiographic Evaluation

X-ray follow-up done

☐ yes ☐ no

Reason:

Notes:

Please fax this page as soon as completed

DataFax #107 Plate #070 Visit #260

smith&nephew	Clinical Follow-up (page 2 of 2)	Project No: R3 Study Patient No: ☐☐ ☐☐☐

5 Years

Harris Hip Score

Hip pain *(Tick one box only)*

- ☐ none or ignores it
- ☐ slight, minimal; no compromise in activities
- ☐ mild; following longer activities
- ☐ moderate; some limitations of activities
- ☐ marked; serious limitations of activities
- ☐ disabled; no activities possible, bedridden

Enter public transportation *(Tick one box only)*

- ☐ yes, possible
- ☐ no, unable

Putting on shoes and socks *(Tick one box only)*

- ☐ with ease
- ☐ with difficulty
- ☐ unable

Distance walked *(Tick one box only)*

- ☐ unlimited, several hours
- ☐ six blocks, up to 2 km
- ☐ daily shopping, up to 500 m
- ☐ indoors only, up to 50 m
- ☐ bed / chair / not able to walk

Support *(Tick one box only)*

- ☐ none
- ☐ single cane for long walks
- ☐ single cane most of the time
- ☐ one crutch
- ☐ two canes
- ☐ two crutches or not able to walk

Stairs *(Tick one box only)*

- ☐ foot over foot, without banister
- ☐ foot over foot, with banister
- ☐ in any manner
- ☐ unable

Sitting *(Tick one box only)*

- ☐ comfortably in any chair 1 hour
- ☐ on a high chair for 1 1/2 hour
- ☐ unable to sit comfortably

Limp *(Tick one box only)*

- ☐ none
- ☐ slight
- ☐ moderate
- ☐ severe

Leg length difference *(Tick one box only)*

- ☐ none
- ☐ ipsilateral longer ☐☐ mm
- ☐ ipsilateral shorter ☐☐ mm

Trendelenburg *(Tick one box only)*

- ☐ unable to test
- ☐ negative
- ☐ indifferent
- ☐ positive

Range of motion *(neutral-zero-method)*

Flex ☐☐☐ / ☐☐ / ☐☐ Ext

Abd ☐☐ / ☐☐ / ☐☐ Add

ER ☐☐ / ☐☐ / ☐☐ IR

Investigator's Signature: _____ Date: ☐☐ (Day) ☐☐ (Month) ☐☐ (Year)

Please fax this page as soon as completed

DataFax # 107 Plate # 081 Visit # 260 5 Year

smith&nephew

Independent Review X-ray Follow-up

(page 1 of 2)

Project No.: R3

Study Patient No: ☐☐ ☐☐☐

Date of Radiograph: ☐☐ ☐☐ ☐☐ Day Month Year

General Findings

Cup position **

- ☐ unchanged
- ☐ migration cranial ☐☐ mm
- ☐ migration medial ☐☐ mm
- ☐ change in inclination ☐☐ °

Stem position **

- ☐ unchanged
- ☐ varus tilted ☐☐ °
- ☐ valgus tilted ☐☐ °
- ☐ subsidence ☐☐ mm

Stem fixation/for uncemented stems (Engh et al)

- ☐ not applicable
- ☐ fixation by bone ingrowth
- ☐ stable fibrous ingrowth
- ☐ unstable implant

****Compared to baseline post-operative**

Heterotopic ossification (Brooker Classification) *(Tick one box only)*

- ☐ Grade 0 none, no islands of bone
- ☐ Grade I islands of bone within the soft tissues about the hip
- ☐ Grade II bone spurs from the pelvis or proximal end of the femur leaving at least 1 cm between opposing bone surfaces
- ☐ Grade III bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm
- ☐ Grade IV apparent bone ankylosis of the hip

Notes:

Investigator's Signature: _____ Date: ☐☐ ☐☐ ☐☐ Day Month Year

Please fax this page as soon as complete

DataFax # 107 Plate # 093 Visit # 260 5 Year

smith&nephew

Independent Review X-ray Follow-up

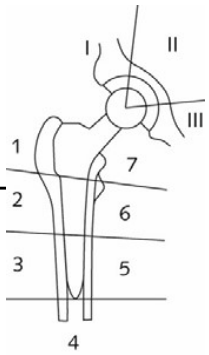
Project No.: R3

Patient No: ☐☐ ☐☐☐

Radiographic Evaluation

AP Cup / LAT

	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone I	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone II	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone III	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone IV	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone V	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone VI	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



AP Stem / LAT

	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	minimal 1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone 1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
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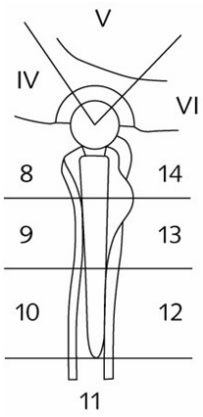
Zone 11	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 12	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 13	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 14	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



Notes:

Investigator's Signature: _____ Date: ☐☐ ☐☐ ☐☐ (Day / Month / Year)

Please fax this page as soon as complete

DataFax #107 Plate #060 Visit #284

smith&nephew	Clinical Follow-up (page 1 of 2)	Project No: R3 Study Patient No: ☐☐ ☐☐☐

7 Years

Date of Assessment: ☐☐ Day ☐☐ Month ☐☐ Year

Clinical follow-up done

☐ yes ☐ no

General Findings

Complications since last visit

☐ no

☐ yes
*Please complete **adverse event** form*

Charnley Classification
(Tick one box only)

☐ A only ipsilateral hip involved

☐ B both hips involved

☐ C other factors affecting locomotion

Patients Opinion

Satisfaction of patient *(Tick one box only)*

☐ very satisfied

☐ satisfied

☐ partly satisfied, partly dissatisfied

☐ dissatisfied

☐ very dissatisfied

Radiographic Evaluation

X-ray follow-up done

☐ yes ☐ no

Reason:

Notes:

Please fax this page as soon as completed

DataFax #107 Plate #070 Visit #284

smith&nephew	Clinical Follow-up (page 2 of 2)	Project No: R3 Study Patient No: ☐☐ ☐☐☐

7 Years

Harris Hip Score

Hip pain *(Tick one box only)*

- ☐ none or ignores it
- ☐ slight, minimal; no compromise in activities
- ☐ mild; following longer activities
- ☐ moderate; some limitations of activities
- ☐ marked; serious limitations of activities
- ☐ disabled; no activities possible, bedridden

Enter public transportation *(Tick one box only)*

- ☐ yes, possible
- ☐ no, unable

Putting on shoes and socks *(Tick one box only)*

- ☐ with ease
- ☐ with difficulty
- ☐ unable

Distance walked *(Tick one box only)*

- ☐ unlimited, several hours
- ☐ six blocks, up to 2 km
- ☐ daily shopping, up to 500 m
- ☐ indoors only, up to 50 m
- ☐ bed / chair / not able to walk

Support *(Tick one box only)*

- ☐ none
- ☐ single cane for long walks
- ☐ single cane most of the time
- ☐ one crutch
- ☐ two canes
- ☐ two crutches or not able to walk

Stairs *(Tick one box only)*

- ☐ foot over foot, without banister
- ☐ foot over foot, with banister
- ☐ in any manner
- ☐ unable

Sitting *(Tick one box only)*

- ☐ comfortably in any chair 1 hour
- ☐ on a high chair for 1 1/2 hour
- ☐ unable to sit comfortably

Limp *(Tick one box only)*

- ☐ none
- ☐ slight
- ☐ moderate
- ☐ severe

Leg length difference *(Tick one box only)*

- ☐ none
- ☐ ipsilateral longer ☐☐ mm
- ☐ ipsilateral shorter ☐☐ mm

Trendelenburg *(Tick one box only)*

- ☐ unable to test
- ☐ negative
- ☐ indifferent
- ☐ positive

Range of motion *(neutral-zero-method)*

Flex ☐☐☐ / ☐☐ / ☐☐ Ext

Abd ☐☐ / ☐☐ / ☐☐ Add

ER ☐☐ / ☐☐ / ☐☐ IR

Investigator's Signature: _____ Date: ☐☐ (Day) ☐☐ (Month) ☐☐ (Year)

Please fax this page as soon as completed

DataFax # 107 Plate # 081 Visit # 284 7 Year

smith&nephew

Independent Review X-ray Follow-up

(page 1 of 2)

Project No.: R3

Study Patient No: ☐☐ ☐☐☐

Date of Radiograph: ☐☐ ☐☐ ☐☐ Day Month Year

General Findings

Cup position **

- ☐ unchanged
- ☐ migration cranial ☐☐ mm
- ☐ migration medial ☐☐ mm
- ☐ change in inclination ☐☐ °

Stem position **

- ☐ unchanged
- ☐ varus tilted ☐☐ °
- ☐ valgus tilted ☐☐ °
- ☐ subsidence ☐☐ mm

Stem fixation/for uncemented stems (Engh et al)

- ☐ not applicable
- ☐ fixation by bone ingrowth
- ☐ stable fibrous ingrowth
- ☐ unstable implant

****Compared to baseline post-operative**

Heterotopic ossification (Brooker Classification) *(Tick one box only)*

- ☐ Grade 0 none, no islands of bone
- ☐ Grade I islands of bone within the soft tissues about the hip
- ☐ Grade II bone spurs from the pelvis or proximal end of the femur leaving at least 1 cm between opposing bone surfaces
- ☐ Grade III bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm
- ☐ Grade IV apparent bone ankylosis of the hip

Notes:

Investigator's Signature: _____ Date: ☐☐ ☐☐ ☐☐ Day Month Year

Please fax this page as soon as complete

DataFax # 107 Plate # 093 Visit # 284 7 Year

smith&nephew

Independent Review X-ray Follow-up

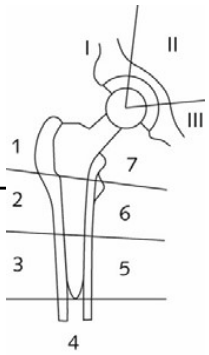
Project No.: R3

Patient No: ☐☐ ☐☐☐

Radiographic Evaluation

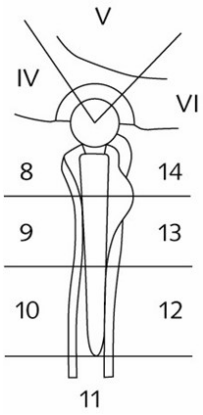
AP Cup / LAT

	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone I	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone II	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone III	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone IV	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone V	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone VI	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



AP Stem / LAT

	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	minimal 1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone 1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 5	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 6	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 7	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 8	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 9	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 10	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 11	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 12	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 13	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 14	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



Notes:

Investigator's Signature: _____ Date: ☐☐ ☐☐ ☐☐ (Day / Month / Year)

Please fax this page as soon as complete

DataFax #107 Plate #060 Visit #320

smith&nephew	Clinical Follow-up (page 1 of 2)	Project No: R3 Study Patient No:

10 Years

Date of Assessment: Day Month Year

Clinical follow-up done

☐ yes ☐ no

General Findings

Complications since last visit

☐ no

☐ yes
*Please complete **adverse event** form*

Charnley Classification
(Tick one box only)

☐ A only ipsilateral hip involved

☐ B both hips involved

☐ C other factors affecting locomotion

Patients Opinion

Satisfaction of patient *(Tick one box only)*

☐ very satisfied

☐ satisfied

☐ partly satisfied, partly dissatisfied

☐ dissatisfied

☐ very dissatisfied

Radiographic Evaluation

X-ray follow-up done

☐ yes ☐ no

Reason:

Notes:

Please fax this page as soon as completed

DataFax #107 Plate #070 Visit #320

smith&nephew	Clinical Follow-up (page 2 of 2)	Project No: R3 Study Patient No: ☐☐ ☐☐☐

10 Years

Harris Hip Score

Hip pain *(Tick one box only)*

- ☐ none or ignores it
- ☐ slight, minimal; no compromise in activities
- ☐ mild; following longer activities
- ☐ moderate; some limitations of activities
- ☐ marked; serious limitations of activities
- ☐ disabled; no activities possible, bedridden

Enter public transportation *(Tick one box only)*

- ☐ yes, possible
- ☐ no, unable

Putting on shoes and socks *(Tick one box only)*

- ☐ with ease
- ☐ with difficulty
- ☐ unable

Distance walked *(Tick one box only)*

- ☐ unlimited, several hours
- ☐ six blocks, up to 2 km
- ☐ daily shopping, up to 500 m
- ☐ indoors only, up to 50 m
- ☐ bed / chair / not able to walk

Support *(Tick one box only)*

- ☐ none
- ☐ single cane for long walks
- ☐ single cane most of the time
- ☐ one crutch
- ☐ two canes
- ☐ two crutches or not able to walk

Stairs *(Tick one box only)*

- ☐ foot over foot, without banister
- ☐ foot over foot, with banister
- ☐ in any manner
- ☐ unable

Sitting *(Tick one box only)*

- ☐ comfortably in any chair 1 hour
- ☐ on a high chair for 1 1/2 hour
- ☐ unable to sit comfortably

Limp *(Tick one box only)*

- ☐ none
- ☐ slight
- ☐ moderate
- ☐ severe

Leg length difference *(Tick one box only)*

- ☐ none
- ☐ ipsilateral longer ☐☐ mm
- ☐ ipsilateral shorter ☐☐ mm

Trendelenburg *(Tick one box only)*

- ☐ unable to test
- ☐ negative
- ☐ indifferent
- ☐ positive

Range of motion *(neutral-zero-method)*

Flex ☐☐☐ / ☐☐ / ☐☐ Ext

Abd ☐☐ / ☐☐ / ☐☐ Add

ER ☐☐ / ☐☐ / ☐☐ IR

Investigator's Signature: _____ Date: ☐☐ (Day) ☐☐ (Month) ☐☐ (Year)

Please fax this page as soon as completed

DataFax # 107 Plate # 081 Visit # 320 10 Year

smith&nephew

Independent Review X-ray Follow-up

(page 1 of 2)

Project No.: R3

Study Patient No: ☐☐ ☐☐☐

Date of Radiograph: ☐☐ ☐☐ ☐☐ (Day Month Year)

General Findings

Cup position **

- ☐ unchanged
- ☐ migration cranial ☐☐ mm
- ☐ migration medial ☐☐ mm
- ☐ change in inclination ☐☐ °

Stem position **

- ☐ unchanged
- ☐ varus tilted ☐☐ °
- ☐ valgus tilted ☐☐ °
- ☐ subsidence ☐☐ mm

Stem fixation/for uncemented stems (Engh et al)

- ☐ not applicable
- ☐ fixation by bone ingrowth
- ☐ stable fibrous ingrowth
- ☐ unstable implant

****Compared to baseline post-operative**

Heterotopic ossification (Brooker Classification) *(Tick one box only)*

- ☐ Grade 0 none, no islands of bone
- ☐ Grade I islands of bone within the soft tissues about the hip
- ☐ Grade II bone spurs from the pelvis or proximal end of the femur leaving at least 1 cm between opposing bone surfaces
- ☐ Grade III bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm
- ☐ Grade IV apparent bone ankylosis of the hip

Notes:

Investigator's Signature: _____ Date: ☐☐ ☐☐ ☐☐ (Day Month Year)

Please fax this page as soon as complete

DataFax # 107 Plate # 093 Visit # 320 10 Year

smith&nephew

Independent Review X-ray Follow-up

(page 2 of 2)

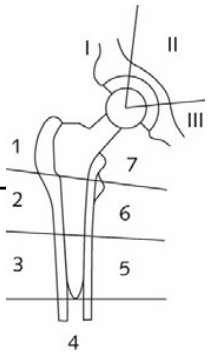
Project No.: R3

Patient No: ☐☐ ☐☐☐

Radiographic Evaluation

AP Cup

	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone I	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone II	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone III	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone IV	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone V	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone VI	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



AP Stem

	Radiolucent lines				Osteolysis		Atrophy				Hypertrophy			
Negative ☐					☐		☐				☐			
	0mm	1mm	2mm	>2mm	no	yes	none	minimal 1mm	moderate 2mm	severe >2mm	none	minimal 1mm	moderate 2mm	severe >2mm
Zone 1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
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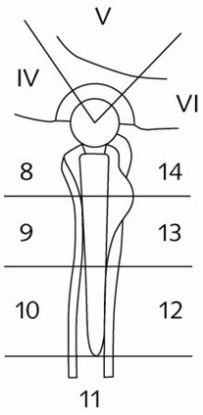
Zone 6	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 7	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 8	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 9	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 10	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 11	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 12	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 13	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Zone 14	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐



LAT _____ AP Cup _____ LAT _____ AP Stem _____

Notes:

Investigator's Signature: _____ Date: ☐☐ ☐☐ ☐☐☐☐ (Day / Month / Year)

Please fax this page as soon as complete

DataFax # 107 Plate # 099

smith&nephew	**Missed Visit/ Telephone Follow-up**	Project No: R3 Study Patient No: ☐☐ ☐☐☐

Interval Missed: ☐ 3 Months ☐ 1 Year ☐ 3 Years ☐ 5 Years ☐ 7 Years ☐ 10 Years

Date of Report: ☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

Use this form for subjects still on study, but who will not be present for their scheduled visit.

Reason Missed: (Tick one box only)

- ☐ Illness
- ☐ Patient on vacation
- ☐ Patient moved
- ☐ Patient address unknown
- ☐ Patient contacted and is feeling fine but does not want to be examined
- ☐ Long difficult traveling distances
- ☐ Business commitments
- ☐ Patient is non-compliant with study requirements
- ☐ Other, please specify: _____

Contact the subject by telephone and confirm the information below. If during the discussion Serious Adverse Events are revealed, complete the Adverse Event and Serious Adverse Event case report forms. Record telephone contact in the medical notes.

Telephone Follow-up

☐ **Unable to contact subject by phone during the visit window** *(No further response required)*

Ask the following questions and record the information.

1. Has any component of your Smith & Nephew modular hip been removed since your last visit?

☐ Yes ☐ No

→ Complete Adverse Event Case Report Form

2. Have you had any problems with the study hip since the last visit to the clinic?

☐ Yes ☐ No

→ Complete Adverse Event Case Report Form

3. Do you expect to have the study device removed during the next year?

☐ Yes ☐ No

→ Request subject to contact study coordinator following the removal of device

4. How satisfied are you with your hip replacement?

☐ Very satisfied ☐ Somewhat satisfied ☐ Somewhat dissatisfied ☐ Very dissatisfied

5. If you had to make the decision again to undergo your hip replacement surgery, would you do it again?

☐ Yes ☐ No

Investigator's Signature: _____ Date: ☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

DataFax # 107 Plate # 300

smith&nephew	**Adverse Event**	Project No: R3 Study Patient No: ☐☐ ☐☐☐

Please complete ONE event form per complication.
Number each event sequentially beginning with "01"

Date of Onset: ☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

Event No: ☐☐

Adverse Event

Event / Diagnosis

please specify: _____

Severity *(Tick one box only)*
☐ mild ☐ moderate ☐ severe

Serious *(Tick one box only)*
☐ no ☐ yes

Involves operated side *(Tick one box only)*
☐ no ☐ yes ☐ not applicable

Relationship to study device
(Tick one box only)
☐ definitely related
☐ probably related
☐ possibly related
☐ not related

Relationship to study procedure
(Tick one box only)
☐ definitely related
☐ probably related
☐ possibly related
☐ not related

Treatment
☐ none
☐ medication/orthotics
☐ Procedure (not study hip related)
☐ procedure (study hip), specify →

Procedure *(Tick one box only)*
☐ invasive or surgical procedure
☐ noninvasive procedure

Outcome of complication *(Tick one box only)*
☐ resolved
☐ ongoing / unresolved
☐ death, date → ☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

Prosthesis in situ at date of death
☐ no, latest date known ☐ Yes
↓
☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

☐ Removal or revision of component(s), date:
↓
☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

Components removed / revised
☐ femoral head
☐ femoral stem
☐ acetabular cup
☐ taper sleeve
☐ acetabular liner

Hospital (inpatient or outpatient) / Readmission required?
☐ no
☐ yes, date of readmission: ☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

Notes: _____
_____

Investigator's Signature: _____ Date: ☐☐ *Day* ☐☐ *Month* ☐☐ *Year*

DataFax #107 Plate #101 Visit #099

smith&nephew	**Study Termination** (page 1 of 1)	Project No: R3 Study Patient No: ☐☐ ☐☐☐

Date of Termination: ☐☐ Day ☐☐ Month ☐☐ Year

Did the patient complete the study?

☐ no ☐ yes

Study Termination Reason

Reason *(Tick one box only)*

☐ patient withdrew consent, date:

☐☐ Day ☐☐ Month ☐☐ Year

☐ patient refuses/can't return, please specify:

_____

☐ patient lost to follow-up after contact attempts were made according to protocol

☐ investigator judgement, please specify:

_____

☐ device revised/removed *please complete **adverse event** form*

☐ patient deceased *please complete **adverse event** form*

☐ other, please specify:

_____

Notes:

My signature signifies that I have reviewed all of the completed CRFs for this patient and I certify that they are accurate to the best of my knowledge:

Investigator's Signature: _____ Date: ☐☐ Day ☐☐ Month ☐☐ Year

Please fax this page as soon as completed

Appendix III

STATISTICAL ANALYSIS PLAN

PROTOCOL: TBD

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

STATISTICAL ANALYSIS PLAN

APPROVAL PAGE

Document Information	
Protocol Number:	TBD
Version:	0.3
Document Date:	11 Jan 2017
Prepared for:	Smith & Nephew
Prepared by:	Hongsuk Song, CROS NT

The Statistical Analysis Plan has been completed and reviewed and the contents are approved for use for the analysis.

Lead Statistician details:	
Name:	Hongsuk Song
Job Role:	Senior Statistician
Company:	CROS NT
Signature:	
Date of signature:	*(DD Mmm YYYY)*

Sponsor Approver details:	
Name:	
Job Role:	
Company:	
Signature:	
Date of signature:	*(DD Mmm YYYY)*

Contents

Abbreviations

AE	Adverse Event
AP	Anteroposterior
CAPA	Corrective and Preventive Action
CoC	Ceramic-on-ceramic
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-polethylene
PMA	Premarket Approval Application
PI	Principal Investigator
PAS	Post-Approval Study
SAE	Serious Adverse Event
THA	Total Hip Arthroplasty
THP	Total Hip Prosthesis
USADE	Unanticipated Serious Adverse Device Effect
XLPE	Cross Linked Polyethylene

Revision History

Document Version	Changes Made	Document Date
0.1	Original	21 October 2016
0.2	Update based on suggestions by FDA (email from Dr. L. Sun dated November 10, 2016)	13 December 2016
0.3	Update based on request by FDA (email from Dr. L. Sun dated January 3, 2017)	11 January 2017

1. Introduction

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.

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).

3. Study Design

3.1 General design and plan

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.

3.2 Visit Schedule and Visit Windows

The intervals and schedule of evaluations are provided in the following table.

Study Activity	Preop	Intra-op	D/C	3M	1Y	3Y	5Y (± 6 Mo)	7Y (± 6 Mo)	10Y (± 6 Mo)
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

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.

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

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.

3.3 Sample size justification

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.

3.4 Randomization and blinding

This is a non-randomized device trial.

3.5 Efficacy endpoints

3.5.1 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%-100.0%). 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.

3.5.2 Secondary efficacy endpoints

Secondary endpoints will be evaluated at 10 years post study procedure and 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°);

3.6 Safety endpoints

Adverse events, noted by study staff and reported by the subject, and occurring from the time of study device implantation through to study completion should be recorded on the appropriate CRFs.

4. Statistical Analysis

4.1 General

Categorical variables will be summarized with the number and percent of subjects in each group. Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum values. 95% confidence intervals will be calculated for the primary and secondary endpoints.
All data collected in the CRF will be presented in the listings.

4.2 Analysis populations

4.2.1 Enrolled set

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.

4.3 Software

SAS® v9.2 or above will be used to analyse the data.

4.4 Handling of missing and incomplete data

The number of patients with missing data will be presented under the "Missing" category, if present.

When continuous data are being summarized, only the non-missing values will be evaluated for computing summary statistics.

A sensitivity analysis will be carried out comparing results of the original analysis to the results of an analysis where all missing data are assumed to be failures.

A second sensitivity analysis will be carried out using multiple imputation of the missing data in the form of a tipping point analysis. Multiple scenarios will be analyzed, each with a different number of missing data points imputed as successes for each treatment group. (Missing data points not imputed as successes will be imputed as failures.) The purpose of the analysis is to find the tipping point where a certain number of success imputations for each treatment group causes the inference to reverse.

In general, partial dates will be imputed as follows:

- if only the day is missing, the first day of the month will be assumed;
- if the day and the month are missing, January 1st will be assumed;
- if a date is completely missing or unknown the patient's data will not be included for analysis

5. Evaluation of Demographic and Baseline Characteristics

Given the nature of this study, the demographic data have been already obtained. The demographic and baseline characteristics will be summarized using descriptive statistics for the Enrolled Set.

6. Patient Accounting

Patient accounting will be presented according to the recommendations in the FDA guidance entitled "Clinical Data Presentations for Orthopedic Device Applications".

- Actual A: Subjects with complete data for the primary endpoint, evaluated per protocol, in the window time frame.
- Actual B: Subjects with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting).
- Theoretical: Number of subjects that would have reached the beginning of the study window associated with each visit if all subjects returned.
- Deaths: Cumulative number of subjects that died during or prior to the study visit.
- Failures: Cumulative number of subjects that failed (revision) during or prior to the study visit.
- Expected: Theoretical subjects minus the number of deaths and revisions.
- Follow-up Rate: Actual A/Expected*100

Patients discontinued from the study prematurely will be presented, with a breakdown of the reasons for discontinuation as reported in the CRF.

7. Evaluation of Efficacy

7.1 Analysis of primary endpoint

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

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.

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).

7.2 Analysis of secondary efficacy 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°) and

These endpoints will be summarized using descriptive statistics and presented for all post-operative visits.

8. Evaluation of Safety

The number of AEs, SAEs, USADEs, Reoperation and Revisions, and the number and the percentage of patients experiencing AEs, SAEs, USADEs will be presented for the enrolled set.

The number of AEs and the number and the percentage of patients with at least one AE will be presented for AEs, and SAEs.

The number and the percentage of patients with at least one AE will be presented by severity, seriousness, device relatedness and procedure relatedness.

8.1 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.

8.2 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.

8.3 Adverse Event Relatedness to Study Device and Study Procedure

All adverse events (AE) are assessed for relatedness to the study device and study procedure based upon the following definition:

- 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.

8.4 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.

8.5 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 any component revisions should be documented on the Adverse Event CRF.

8.6 Assessment of Adverse Event Severity

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.

9. Protocol violations

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.

A listing of protocol deviations will be provided.

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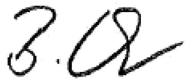
PROTOCOL APPROVAL FORM

Study Title:	**A prospective, multicenter, non-randomized, clinical outcomes study of the R3◊ Acetabular System in patients with degenerative hip disease**
Protocol Number:	R3H01/02/01/2017/Version 2.0 /BNA (including Post-Approval Study of the R3 Biolox delta Ceramic Acetabular System – Europe)
Protocol Date:	February 01, 2017
Protocol Version:	2.0
Documents Attached:	☐ Initial Study Protocol x Amended Study Protocol
Author (Name/Role):	Nicole Steinfelder /CSM

Approval Position	Approver Name	Approver Signature	Date Approved
Head of Global Biostatistics			
Head of Global Clinical Operations			
Head of Global Clinical Strategy	Beate Hanson		20.02.2017
Medical Monitor (as applicable) ☒ Not applicable			
Regulatory representative (for studies involving non-finished S& N products) ☒Not applicable			

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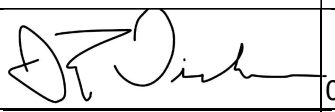
Approval Position	Approver Name	Approver Signature	Date Approved
Head of Global Biostatistics			
Head of Global Clinical Operations	Jaime E. Dickerson		08 FEB 2017
Head of Global Clinical Strategy			
Medical Monitor (as applicable) ☒ Not applicable			
Regulatory representative (for studies involving non-finished S& N products) ☒Not applicable			

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Head of Global Biostatistics	Alan Rossington		13 Feb 2017
Head of Global Clinical Operations			
Head of Global Clinical Strategy			
Medical Monitor (as applicable) ☒ Not applicable			
Regulatory representative (for studies involving non-finished S& N products) ☒Not applicable			