Post-Approval Study of the R3™ Biolox® delta Ceramic Acetabular System – United States

Protocol Number:	16-4565-10
Protocol Date:	14DEC2023
Protocol Version:	Version 6.0
Study Product Name:	R3 delta Ceramic Acetabular System
Sponsor:	Smith & Nephew, Inc. 7135 Goodlett Farms Parkway Cordova, TN 38016 US

Nondisclosure Statement

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SPONSOR APPROVAL

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ABBREVIATIONS & DEFINITIONS

AE	Adverse Event
ADE	Adverse Device Effect
ASA	American Society of Anesthesiologists
AP	Anteroposterior
BMI	Body Mass Index
CAPA	Corrective and Preventive Action
CoC	Ceramic-on-ceramic
CRF	Case Report Form
CCGs	Case Report Form Completion Guidelines
CV	Curriculum Vitae
DOD	Biolox delta ceramic-on-ceramic
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
mHHS	Modified Harris Hip Score
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IRB	Institutional Review Board
OUS	Outside of the United States
PAS	Post-approval study
PMA	Premarket Approval
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SADE	Serious Adverse Device Effect
THA	Total Hip Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect

Protocol Synopsis:

Title of Study:	Post-Approval Study of the R3™ Biolox® delta Ceramic Acetabular System – United States
Study Type:	Post-market Outcomes Study
Study Device:	R3™ delta Ceramic Acetabular System
Indications	The R3 delta 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
Primary Endpoint:	The primary study endpoint is overall success at 3 Years postoperative, defined as: • No component revision, • Modified Harris Hip Score (mHHS) of at least 80 points, and • No radiographic failure, defined as: No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, no femoral or acetabular subsidence greater than or equal to 5 mm from baseline, and no acetabular cup inclination changes greater than 4 degrees from baseline when accompanied by a “Mild”, ”Moderate”, Marked”, or ”Disabled” mHHS pain score.
Secondary Endpoints:	Secondary endpoints include clinical assessments of pain and function using the modified Harris Hip Score, radiographic findings and implant survivorship.
Length of Study:	The expected timeline for the study is a total of approximately 6 years: • Study enrollment commenced in February 2018. • Average enrollment of 10 subjects per month. • Study enrollment completed October 2019. • Study data collection completed by May 2023. • The final study report is to be submitted in March 2024.
Number of Sites:	up to 10 sites
Sample Size:	183 Subjects
Inclusion Criteria:	1. Patient is 18-75 years old and he/she is skeletally mature 2. Patient requires primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis.

	3. 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 4. Patient is willing and able to participate in required follow-up visits and to complete study procedures and questionnaires 5. Patient has consented to participating in the study by signing the IRB/EC approved informed consent form
Exclusion Criteria:	1. Patients with insufficient quantity or quality of bone support; metabolic bone disease; osteoporosis 2. Patients with neurological or muscular conditions that would place extreme load or instability upon the hip joint 3. Patients with active joint infections or chronic systemic infection 4. Obese patients where obesity is defined as BMI $\geq$ 40 5. Skeletal immaturity 6. Known allergy to implant materials

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 Acetabular System in patients with degenerative hip disease in Europe. The study design included an evaluation of the performance of a Biolox delta ceramic-on-ceramic cohort using the R3 delta Ceramic Acetabular System in patients undergoing primary total hip arthroplasty. The R3 Biolox delta Ceramic Acetabular System has been commercially available outside the United States (OUS) since 2008 and this study satisfied post-market surveillance requirements in Europe. Clinical data from this European post-market study was used to support a Premarket Approval (PMA) application that was submitted to the US Food and Drug Administration (FDA) on August 20, 2015. The clinical data submitted in the PMA application (PMA cohort) included subject follow-up to the 3 year postoperative interval. Approval was sought for the R3 delta Ceramic Acetabular System based upon the PMA cohort clinical data. The PMA (P150030) was reviewed by the FDA and approved on October 17, 2016. The R3 delta Ceramic Acetabular System is commercially available in the United States. A condition of the FDA approval was that Smith & Nephew Orthopaedics was required to sponsor a post-approval study (PAS) of the R3 delta Ceramic Acetabular System in the United States to address any concerns regarding differences in the US and European patient populations.

1.2. Study Rationale

This study is being conducted to comply with FDA requirements that Smith & Nephew Orthopaedics sponsor a post-market study of the R3 delta Ceramic Acetabular System in the US.

2. STUDY OBJECTIVES

The primary objective is to confirm that the safety and effectiveness of the R3 Biolox delta Ceramic Acetabular System in the US population is consistent with the effectiveness and safety profile shown in the European study (PMA cohort).

2.1. Primary Endpoint

The primary endpoint is overall study success at 3 years postoperative. Success is defined the same way it was in the PMA cohort, to allow comparison. Overall success is defined as:

- No component revision,
- Modified Harris Hip Score (mHHS) of at least 80 points, and
- No radiographic failure, defined as:

  No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, no femoral or acetabular subsidence greater than or equal to 5 mm from baseline, and no acetabular cup inclination changes greater than 4 degrees from baseline when accompanied by a “Mild”, “Moderate”, ”Marked” or “Disabled” mHHS pain score.

2.2. Secondary Endpoints

Secondary endpoints include clinical assessments of pain and function using the modified Harris Hip Score, radiographic findings and implant survivorship.

3. Study Design

This is a post-market, prospective, multicenter, observational study to collect clinical and radiological data from 183 subjects undergoing primary total hip arthroplasty with the R3 delta Ceramic Acetabular System.

Total study duration for study participants will be 3 years with follow-up visits planned prior to hospital discharge, and at 3 months, 1 year, 2 years and 3 years postoperative. Subjects will be enrolled at up to 10 sites in the United States.

4. Study Device

The R3 delta Ceramic Acetabular System is a ceramic-on-ceramic (CoC) hip prosthesis composed of modular components that include a R3 porous coated acetabular shell, a zirconia toughened alumina (delta) ceramic acetabular liner, and a zirconia toughened alumina (delta) ceramic femoral head and one of four titanium alloy femoral stems. All implantable devices are for single use.

R3 Acetabular Shell/Cup

The R3 acetabular shells are compatible only with R3 acetabular liners. The R3 acetabular shells are manufactured from Ti-6Al-4V (ASTM F 1472 and ISO 5832-3). There are eleven (11) sizes of acetabular shells available, ranging from 48 mm through 68 mm outer diameters in 2 mm increments. Each shell features an apex hole to accept the cup positioner / impactor instrument. Shells have either no screw holes or three screw holes arranged about the apex hole. These holes are for optional, adjunctive screw fixation to the superior acetabulum with Spherical Head Screws, which are available in lengths of 15-70mm in 5mm increments. Screws are self-tapping, but the screw holes in the acetabulum need to be pre-drilled to the minor diameter of the screw. Hole covers are available to cover unused screw holes, if desired. Screws and hole covers are manufactured from Ti-6Al-4V ELI (ASTM F 136). The interior of the R3 Acetabular Shell features a female taper which is designed for mechanical assembly to the male taper of the outer titanium ring of the mating R3 delta Ceramic Liner. The outer shell geometry is hemispherical and feature a sintered asymmetric porous coating (STIKTITE™) manufactured from commercially pure titanium powder (ASTM F 67 and ISO 5832-2).

R3 Acetabular Liner/Insert

The delta ceramic acetabular liners are manufactured from Biolox delta zirconia toughened alumina ceramic and feature a titanium (ASTM F1472 and ISO 5832-3) outer ring. They are available in ten sizes.

Femoral Head

The zirconia toughened alumina ceramic ball heads are manufactured from Biolox delta zirconia toughened alumina ceramic. The ceramic ball heads are available in six (6) sizes: three (3) heads with an outer diameter of 32 mm and three (3) heads with an outer diameter of 36mm. Each diameter head size has three different neck lengths, short (+0), medium (+4), and long (+8) for proper anatomic and musculature fit. Externally, all ball heads

are highly polished. All ball heads conform to the 12/14 cone taper of the femoral stems. The zirconia toughened alumina ceramic heads lock onto the machined hip stem taper and do not rotate on the stem. The 32mm and 36mm delta ceramic femoral heads are used with R3 delta Ceramic Acetabular Liners of corresponding internal diameters.

The R3 delta Ceramic Acetabular System is approved for use with the 12/14 taper of Smith & Nephew's legally marketed titanium alloy (ASTM F1472) cementless SYNERGY™ porous hip stems (Standard and High Offset versions), titanium alloy (ASTM F1472) cementless POLARSTEM™ Collarless Ti/HA hip stems (Standard and Lateral versions), titanium alloy (ASTM F1295) cementless SL-PLUS™ femoral stems (Standard and Lateral versions), and titanium alloy(ASTM F1472) cementless ANTHOLOGY™ porous hip stems (Standard and High Offset versions). The R3 delta Ceramic Acetabular System product Instructions for Use (IFU) provides femoral stem product compatibility information. A copy of the IFU is included in Appendix IV.

The following table shows the head, liner and shell size compatibility:

R3 Ceramic Liners Compatibility			
Head Catalog Item Number (Head Offset)	**Head size**	**Liner Catalog Item Number**	**OD/shell size**
71325171 (+0) 71325172 (+4) 71315173 (+8)	32mm	71325148	48mm
		71325150	50mm
71325174 (+0) 71325175 (+4) 71325176 (+8)	36mm	71325152	52mm
		71325154	54mm
		71325156	56mm
		71325158	58mm
		71325160	60mm
		71325162	62mm
		71325164	64mm
		71325166	66/68mm

The following tables show catalog numbers and sizes of the hip stems approved for use with the R3 delta Ceramic Acetabular System:

SYNERGY™ porous hip stems		
Size	Standard Offset Catalog Item Number	High Offset Catalog Item Number
9	7130-6609	7130-6109
10	7130-6610	7130-6110
11	7130-6611	7130-6111
12	7130-6612	7130-6112
13	7130-6613	7130-6113
14	7130-6614	7130-6114
15	7130-6615	7130-6115
16	7130-6616	7130-6116
17	7130-6617	7130-6117
18	7130-6618	7130-6118

POLARSTEM™ Collarless Ti/HA hip stems		
Size	Standard with Ti/HA Catalog Item Number	Lateral with Ti/HA Catalog Item Number
0	75100463	-----
1	75100464	75100474
2	75100465	75100475
3	75100466	75100476
4	75100467	75100477
5	75100468	75100478
6	75100469	75100479
7	75100470	75100480
8	75100471	75100481
9	75100472	75100482
10	75100473	75100483
11	75100509	75100510

SL-PLUS™ femoral stems		
Size	Standard Catalog Item Number	Lateral with Ti/HA Catalog Item Number
01	75002717	-----
0	75002719	-----
1	75002695	75002748
2	75002697	75002750
3	75002699	75002752
4	75002701	75002756
5	75002703	75002758
6	75002705	75002760
7	75002707	75002762
8	75002709	75002764
9	75002711	75002766
10	75002713	75002768
11	75002714	75002769
12	75002715	75002770

ANTHOLOGY™ porous hip stems		
Size	Standard Offset (Porous) Catalog Item Number	High Offset (Porous) Catalog Item Number
1	7135-6001	7135-6101
2	7135-6002	7135-6102
3	7135-6003	7135-6103
4	7135-6004	7135-6104
5	7135-6005	7135-6105
6	7135-6006	7135-6106
7	7135-6007	7135-6107
8	7135-6008	7135-6108
9	7135-6009	7135-6109
10	7135-6010	7135-6110
11	7135-6011	7135-6111
12	7135-6012	7135-6112
13	7135-6013	7135-6113
14	7135-6014	7135-6114

4.1. Surgical Technique

All study related procedures with the R3 delta Ceramic Acetabular System must be performed according to the recommended surgical technique described in the labeling and in the IFU.

Surgeons selected to participate in this study will be familiar with implanting ceramic hip arthroplasty implants and have evidence of training and expertise in performing total hip arthroplasty procedures.

5. STUDY POPULATION

5.1. Subject Screening & Enrollment

To eliminate the potential for selection bias, Investigators should consecutively pre-screen all subjects undergoing planned total hip arthroplasty with the R3 delta Ceramic Acetabular System. In order to do so, only the existing information obtained per standard routine medical procedures will be used. No study-specific screening procedures, activities or questionnaires will be performed during pre-screening.

Once a subject has completed the informed consent procedure and signed the Informed Consent Form, the Investigator or delegated study research staff can complete the screening process with the subject.

All potential subjects who undergo the pre-screening process will be documented on a Screening and Enrollment Log, on which the date of informed consent or reasons for study exclusion should be noted.

5.2. Subject Inclusion Criteria

Subject must meet all of the following inclusion criteria in order to be enrolled in this study.

1. Patient is 18-75 years old and he/she is skeletally mature
2. Patient requires primary total hip arthroplasty due to non-inflammatory arthritis (degenerative joint disease) such as osteoarthritis, avascular necrosis, or traumatic arthritis
3. 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
4. Patient is willing and able to participate in required follow-up visits and to complete study procedures and questionnaires
5. Patient has consented to participating in the study by signing the IRB/EC approved informed consent form

5.3. Subject Exclusion Criteria

A subject cannot be enrolled in the study if they meet any of the following exclusion criteria.

1. Patients with insufficient quantity or quality of bone support; metabolic bone disease; osteoporosis
2. Patients with neurological or muscular conditions that would place extreme load or instability upon the hip joint
3. Patients with active joint infections or chronic systemic infection
4. Obese patients where obesity is defined as BMI $\geq$ 40

5. Skeletal immaturity
6. Known allergy to implant materials

6. STUDY PROCEDURES

6.1. Study Schematic

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

Study Activity	Pre-operative	Intraoperative (Day 0)	Discharge	3 mo (+/- 2 wks)	1 yr (+/- 2 mo)	2 yr (+/- 2 mo)	3 yr (+/- 2 mo)
Informed Consent	X						
Inclusion/exclusion	X						
Demographics	X						
Operative Data Collection		X					
Discharge Data Collection			X				
Modified Harris Hip Score	X			X	X	X	X
X-rays[1]: AP pelvis, AP hip, lateral hip			X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X	X
Concomitant Medications, Procedures		X	X	X	X	X	X
Telephone Follow Up[2]				*	*	*	*
End of Study/Exit	*	*	*	*	*	*	*

* As needed

[1] see Appendix II- Radiographic Evaluation Protocol

[2] As needed please refer to section 6.5 (Telephone Follow-Up)

6.2. Visit 1: Pre-operative Visit

Information will be collected on the study population prior to device implantation. Demographic factors including age, gender, race and primary diagnosis will be obtained.
Procedures to be completed at the pre-operative visit:

- confirm informed consent and inclusion/exclusion criteria are met
- assign a subject ID
- collect data per case report form (CRF) completion guidelines, including demographic data, mHHS, Charnley Classification, ASA score (American Society of Anesthesiologists), and prior hip surgery
- Perform all study procedures per study schematic

6.3. Visit 2: Intraoperative to Hospital Discharge

Information on the operative procedure for each subject including surgical approach, component size and device identifier, surgical time, and intraoperative blood loss will be obtained. Additionally length of hospital stay and discharge to home or any other institution will be recorded. Any adverse events (complications) occurring from the time of study device implant and prior to discharge will be collected and recorded on the appropriate CRF.

Patients will have radiographs taken after implantation (before discharge from the hospital) to establish a baseline. All study radiographs (Anteroposterior (AP) pelvis, AP hip, and lateral hip) should be acquired according to the Image Acquisition Protocol and will be transmitted to the central imaging vendor for independent review.

6.4. Visit 3: Postoperative

Postoperative follow-up visits will occur at 3 months (+/- 2 weeks), 1 year (+/- 2 months), 2 years (+/- 2 months) and 3 years (+/- 2 months) postoperative. Subjects will be evaluated using the modified Harris Hip Score (mHHS) that was used in the original European post-market surveillance study. The mHHS includes a modification to the "Distance Walked" section of the Harris Hip Score to add distances to the choices available, such as indicating the number of blocks as a defined distance since the term "blocks" is not commonly used as a measurement of distance in Europe. The mHHS should be completed prior to the adverse event assessment when feasible. A copy of the study CRFs is included in Appendix III.

AP and lateral radiographs will be taken at these postoperative visits. All study radiographs (AP pelvis, AP hip, lateral hip) should be acquired according to the Image Acquisition Protocol. X-rays will be transmitted to the central imaging vendor for independent review. Radiographs will be evaluated by an independent evaluator according to the Smith & Nephew Radiographic Evaluation Protocol included in Appendix II.

Procedures to be completed at the postoperative visits:

- perform study procedures per study schematic
- perform required X-rays (see Appendix II for subject positioning details)
- transmit X-rays to the central imaging vendor
- obtain and record any adverse events (AEs) occurring from the time of study device implantation
- collect data per CRF completion guidelines

6.5. 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 device is in place or has been revised, and asked whether any adverse events have occurred since the last visit.

7. Subject Completion and Disposition

7.1. Screening

Subjects considered potential candidates for the study based on pre-screening will sign an IRB/EC approved Informed Consent Form (ICF) prior to any study activities. The Investigator or delegated study research staff may then complete the first study visit with the subject.

7.2. Enrolled Subject

Subject enrollment occurs at the time of surgery. Every subject that receives the study device will be considered enrolled in the study. If a subject has provided consent and completed screening, and for any reason does not receive the study device, the subject will not be considered enrolled in the study. Pre-operative CRFs will not be submitted to the Sponsor until the subject is actually enrolled (treated with the study device) in the study.

7.3. Conditions for Study Termination

All reasonable efforts should be made to retain the subjects for the 3 year duration of this study. If the subject has a revision of any component the subject will be terminated from the study.

A. Screening Failure

If a subject has provided consent, completed screening, and for any reason does not receive the study device, the subject will not be considered enrolled in the study. For these subjects an End of Study: Subject Disposition form needs to be completed and submitted to the Sponsor. Pre-operative, operative, and discharge forms do not need to be submitted.

B. Voluntary Withdrawal

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

C. Lost to Follow-Up

Some actively enrolled subjects will not return for follow-up exams due to a variety of reasons. Study personnel must 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 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 that documentation should be kept with the subjects CRFs. 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.

D. 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
- the Investigator or the Sponsor stops the study for any reason

For each case, information will be obtained on the End of Study: Subject Disposition Form, detailing circumstances leading to the withdrawal.

E. 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
- failure to enroll subjects
- major protocol deviations
- inaccurate or incomplete data
- unsafe or unethical practices
- safety or performance considerations
- Investigator voluntarily or involuntarily discontinues participation in study

8. SAFETY REPORTING

Adverse events and device deficiencies, 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 and reported as below. Adverse event definitions are as per ISO 14155:2011.

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.

This definition includes but is not limited to:

- events related to the study device
- events related to the procedures involved

B. Serious Adverse Event (SAE)

A SAE is an adverse event that:

- resulted in 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. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device [2].

This definition includes:

- adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device
- any event resulting from use error or from intentional misuse of the investigational medical device.

D. Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [2].

E. 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.

F. Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

For the purpose of this study, device deficiencies should be reported when they concern any component of the study device as well as its packaging and tools that need to be used during implantation according to the Instructions for Use.

G. Revisions

A specially designed Study Implant Disposition (Hip) Form will be used in addition to the Adverse Event Form, to document in detail revisions of any of the components of the study device.

8.2. Safety: Investigator's Responsibilities

Investigators shall record adverse events and observed device deficiencies, together with an assessment of seriousness, severity, and device/procedure relatedness, in the subject's source data. Following, Investigators are responsible for documenting AEs and device deficiencies on the appropriate CRF and submitting them to the Sponsor according to the timelines described here below.

At each contact with the subject, the Investigator must seek information on AEs by specific questioning and, as appropriate, by assessment of the subject. AEs must be recorded in standard English medical terminology.

Unresolved AEs should be followed by the Investigator until the events are resolved, the subject is lost to follow-up or through to the end of the study, whichever timing occurs first. Unresolved AEs at the end of the subject's participation will be monitored by the Investigator as part of the site's normal standard of care.

The Investigator will 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 wellbeing. 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 describing the relationship of the AE to the study device/procedure based on the following definitions:

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

8.3. Timelines for Submission of Safety Information:

The timelines begin when the Investigator becomes aware of the event.

The Investigator will report to the Sponsor:

- As soon as possible, but no greater than **24 hours upon becoming aware of the event, SAEs, SADEs, U(S)ADEs and device deficiencies that could have led to a SADE**:
    - if suitable action had not been taken

- if intervention had not been made, or
- if circumstances had been less fortunate

- **Revisions**, **within 24 hours upon becoming aware of the event.** Sponsor will provide an explant retrieval kit on becoming aware of a revision and ask the Investigator to return any revised components for retrieval analysis.

Investigators may also be asked to supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event. Investigators will be responsible for complying with the adverse event reporting requirements of the IRB/EC at the study site.

8.4. Safety reporting: Sponsor's Responsibilities

Sponsor will provide progress reports on safety events to the Investigator to report to the IRB/EC as required. The Sponsor will also, in case of SADEs and device deficiencies that could have led to SADEs, 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

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. The primary endpoint will be analyzed using the exact binomial test method.

A complete Statistical Analysis Plan (SAP) is included in Appendix IV.

9.2. Sample size calculation

The primary objective of this study is to confirm that the safety and effectiveness of the R3 Biolox delta Ceramic Acetabular System in the US population is consistent with the effectiveness and safety profile shown in the European study (PMA cohort). The primary endpoint is overall study success at 3 years postoperative. Secondary endpoints include clinical assessments of pain and function, radiographic findings and survivorship.

Overall success (as defined in the section entitled "Data Collection: Study Endpoints") in the PMA Cohort was found to be 86.4% at 3 years post-surgery for the Biolox delta ceramic-on-ceramic (DOD) treatment group. It is expected that the overall success for the DOD US Cohort is similar to the overall success to the DOD PMA Cohort (European data).

Statistical Hypotheses:

$$H_0: \pi_{DOD} - 0.864 \leq \delta$$

$$H_a: \pi_{DOD} - 0.864 > \delta$$

Where,

π_{DOD} = Overall Success of DOD US

1-sided alpha error = 5%

Power of the test = 80%

δ=-0.08

The minimum sample size required for hypothesis testing: 146 DOD US subjects. The total sample size after adjustment for lost-to-follow-up (20%) is 183 DOD subjects. Sample size was calculated assuming use of an Exact Binomial test [1].

10. ETHICAL CONSIDERATIONS

10.1. Ethical Approval

In accordance with the Declaration of Helsinki and local regulations of the participating countries, sites must gain written IRB/EC approval prior to enrolling research participants in the study.

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 US FDA and IRB/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 Central IRB and IRB/EC of the study site by the Investigator for active sites.

10.3. Informed Consent

All study subjects must sign an IRB/EC approved ICF according to ISO14155:2011 guidelines, GCP guidelines and all applicable national regulations. Potential subjects 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 subject shall have sufficient opportunity to consider participation in the study; a subject cannot be led to believe that they are waiving their rights as a subject or the liability of the Sponsor or Investigator. Subjects are then invited to sign and date the consent form, indicating their consent for enrollment. The Investigator will retain the original copy of the signed consent form in the study files. A duplicate copy shall be provided to the subject.

10.4. Risk – Benefit Analysis

A. Study Related Risks

The study involves the standard assessment of a primary total hip arthroplasty (THA) procedure. The R3 delta Ceramic Acetabular System has been approved for use by the FDA and will be used according to its labeling.

Potential Complications Associated with Any Total Hip Arthroplasty surgery:

- Excessive wear of the implant components secondary to impingement of components or damage of articular surfaces
- Fracture, migration, loosening, subluxation, or dislocation of the prosthesis or any of its components; any of which may require a second surgical intervention or revision;
- Increased hip pain and/or reduced hip function
- Bone fractures
- Osteolysis and/or other peri-prosthetic bone loss
- Metal sensitivity reactions or other allergic/histological reactions to implant material
- Vascular damage resulting in significant blood loss, or
- Neurologic injury resulting in transient or permanent functional and/or sensory deficits
- Leg length change/discrepancy
- Deep venous thrombosis
- Pulmonary or vascular embolism
- Superficial or deep infection, delayed wound healing
- Periarticular calcification
- Myocardial infarction
- Gastrointestinal complications
- Genitourinary complications
- Decreased range of motion
- Aggravation of other joint or back conditions (due to positioning during surgery, postoperative leg length discrepancy, muscular deficiencies, etc.)
- Death

Potential Complications Associated with Ceramic on Ceramic Hip Systems:

- Due to the materials of the device, these may include, but are not limited to, femoral head breakage, acetabular insert (liner) fracture, and device related noise such as squeaking. Other adverse events, common to other hip systems may also occur but at different frequencies.

Possible risks that may occur as a result of study procedures are:

- 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.

Risks related to the general surgical procedures are not considered here because these could be present regardless of participation into the study.

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 arthroplasty.

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, memoranda, dispensing records, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection reports and shipment records and research subject files.

The Investigator shall ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical study and if they completed per protocol or discontinued early and the reason.

All data recorded on the CRF and submitted to the Sponsor must have a corresponding entry in the subject's source documentation that provides detailed evidence of the assessment. The following assessment is an exception: Subject-reported outcome measures (subject-completed sections of the mHHS) may be entered directly on the CRF.

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, IRB/EC and regulatory agencies with direct access to all source data/documents to permit study-related monitoring, audits, IRB/EC review, and regulatory inspections.

11.3. Site Qualification Visit

A site qualification visit may be performed by the Sponsor prior to the execution of a clinical agreement to ensure that all Investigators have the appropriate training, staff, facilities and resources to adequately conduct the study.

11.4. Site Initiation Visit

A site initiation visit to provide training on the specifics of the study, site obligations and expectations of study conduct will be performed by the Sponsor. No screening or other study procedures may be performed prior to the execution of the Clinical Study Agreement and documented IRB/EC approval.

11.5. Interim Monitoring Visits

The Sponsor or its designee will conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with currently approved protocol, with GCP regulations, and with applicable regulatory requirements. Detailed monitoring requirements will be documented within the Clinical Monitoring Plan for this study.

11.6. Sponsor Audits and Regulatory Inspection

The Sponsor, Sponsor's agents, IRB/EC and regulatory agencies may audit study data. The site must accommodate audit requests, notify the Sponsor of any requests as soon as they are received, and provide direct access to study records during the audit.

11.7. 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. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements regarding records retention and IRB/EC reporting requirements.

11.8. Data Handling and Record Keeping Requirements

Case report forms will be supplied by the Sponsor. Subjects will be identified by a subject ID and subject 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, as specified in the Case Report Form Completion Guidelines (CCGs).
Data required according to this protocol are to be recorded on the CRFs at the time of the scheduled visits. Once a subject is enrolled, completed CRFs should be sent to the Sponsor, via entry into the study database in the timeline specified in the CCGs.

11.9. 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. For discontinued product, the essential documents will be retained until at least 2 years have elapsed since the formal discontinuation (via notification of the FDA or other regulatory agency) of clinical development of the study product. 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: deviations from inclusion/exclusion criteria, endpoint variable criteria, and missed study visits or visits outside the window.

12.1. Protocol Deviation Reporting Requirements

Deviations must be reported to the Sponsor through the Protocol Deviation Log 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 IRB/EC of the study site as per their reporting requirements.

Investigators and all study staff (staff at site and at Sponsor) are responsible for ensuring adherence to the 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

The Sponsor will submit reports to the US FDA every six months for the first two years of the study and then annually after that until study completion. A final study report will be submitted to the US FDA three months after the last subject has reached the end of follow-up and final data is collected. Any required extension to the final study report will be agreed upon between the Sponsor and the US FDA. An interim data release will occur at the midpoint of the study, 2.5 years after study initiation. The interim data release will be comprised of data regarding secondary endpoints.

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

BIBLIOGRAPHY

1. https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_power_a0000000996.htm

2. ISO 14155:2011 (2011) Clinical investigation of medical devices for human subjects – Good Clinical Practice.

Addendum 1: Protocol Revision History

Version Date: 25AUG2016
Original Version Number: 0.1

Version Date: 26SEP2016
Version Number: 0.2

Version Date: 03OCT2016
Version Number: 0.3

Version Date: 01MAR2017
Version Number: 0.4

Version Date: 31MAY2017
Version Number: 1.0

Version Date: 10AUG2017
Version Number: 2.0

Version Date: 24OCT2017
Version Number: 3.0

Version Date: 02MAY2018
Version Number: 4.0

Version Date: 29NOV2018
Version Number: 5.0

Version Date: 14DEC2023
Version Number: 6.0

- Summary of Change:
  - Protocol was amended to clarify the primary endpoint based upon discussions between the Sponsor and the US FDA. Administrative updates were also addressed: embedded Sponsor Approval section, length of study, timing of reports, and clarification of CRF completion in the study database.
  - As a result of the protocol amendment, the Radiographic Evaluation Protocol and Statistical Analysis Plan appendices were also amended.