# A Multi-Center, Randomized Controlled Study of Efficacy and Safety of the OXINIUM◊ DH Total Hip Replacement System in Subjects with Non-Inflammatory Arthritis

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| Protocol Number: | 2012-ODH-86 |
| Protocol Date: | 06Oct2023 |
| Study Product Name: | OXINIUM◊ DH Hip System |
| IDE Approval: | G130072 |
| Sponsor: | Smith & Nephew, Inc.<br>1450 E. Brooks Road<br>Memphis, TN 38116<br>USA |

**Note**. This Investigational Protocol is created in reference to:

- Design Considerations for Pivotal Clinical Investigations for Medical Devices. Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff from November 7, 2013.
- Guidance for Industry, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff. FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations from August 14, 2014;
- Guidance for Industry. Adaptive Design Clinical Trials for Drugs and Biologics from November 2019;
- Guidance for Industry. Non-inferiority Clinical Trials from November 2016;
- Guidance for Industry. E6(R2) Good Clinical Practice: Consolidated guidance from March 2018;
- Guidance for Industry. E9 Statistical Principle for Clinical Trials.
- Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection from , January 2009
- ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice

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# 1 Abbreviations

**Table 1: Abbreviations**

| | |
|---|---|
| **ADL** | Activities of Daily Living |
| **AE** | Adverse Event |
| **ANCOVA** | Analysis of covariance |
| **ANOVA** | Analysis of variance |
| **AP** | Anteroposterior |
| **ASTM** | American Society for Testing and Materials |
| **CoC** | Ceramic-on-ceramic |
| **CoP** | Ceramic-on-polyethylene |
| **CRF** | Case Report Form |
| **CT** | Computed Tomography |
| **EC** | Ethical Committee |
| **EQ-5D-3L** | EuroQol 5D 3 Level |
| **EU** | European Union |
| **FDA** | Food and Drug Administration |
| **FJS-12** | Forgotten Joint Score-12 |
| **GCP** | Good Clinical Practice |
| **HHS** | Harris Hip Score |
| **HOOS** | Hip Disability and Osteoarthritic Outcome Scores |
| **HREC** | Human Research Ethics Committee |
| **IC** | Informed Consent |
| **ICH** | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IDE** | Investigational Device Exemption |
| **IRB** | Institutional Review Board |

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|---|---|
| **ITT** | Intention to Treat Population |
| **LVCF** | Last Value Carrying Forward |
| **MAR** | Missing at Random |
| **MARS** | Metal Artifact Reduction Sequence |
| **MCAR** | Missing Completely at Random |
| **MITT** | Modified Intent to Treat |
| **MoM** | Metal-on-metal |
| **MoP** | Metal-on-polyethylene |
| **MRI** | Magnetic Resonance Imaging |
| **NIDJD** | Non-inflammatory Degenerative Joint Disease |
| **nMAR** | Not Missing at Random |
| **ODH** | OXINIUM◊ DH |
| **OUS** | Out-of-United States |
| **PP** | Per-protocol Population |
| **QoL** | Quality of Life |
| **REB** | Research Ethics Board |
| **SADE** | Serious Adverse Device Effect |
| **SAE** | Serious Adverse Event |
| **THA** | Total Hip Arthroplasty (does not include revision surgery) |
| **UCLA** | University of California Los Angeles |
| **VAS** | Visual Analog Scale |
| **UADE** | Unanticipated Adverse Device Effect |
| **WOMAC** | Western Ontario and McMaster Universities Osteoarthritis Index |
| **WOMACFS** | WOMAC Functional Score |
| **XLPE** | Cross Linked Polyethylene |

# 2 Approvals

**Table 2: Approvals**

| Role | Job Title | DocuSign Stamp |
|---|---|---|
| Head of Global Biostatistics and Data Science | Jay Jantz<br>Director, Global Biostatistics and Data Science | DocuSigned by:<br>Jay Jantz<br>Signer Name: Jay Jantz<br>Signing Reason: I approve this document<br>Signing Time: 06-Nov-2023 \| 15:53:55 GMT<br>B7D37248838E4CACAE11E7E55198A88D |
| Head of Global Clinical Affairs | Matthew Christensen<br>Sr. Vice President, Global Clinical and Medical Affairs | DocuSigned by:<br>Matthew Christensen<br>Signer Name: Matthew Christensen<br>Signing Reason: I approve this document<br>Signing Time: 02-Nov-2023 \| 20:09:01 GMT<br>9CA29354DDF6446DB49D00024793ADD4 |
| Global Clinical Operations | Karlie Morgan<br>Regional Clinical Operations Manager, US | DocuSigned by:<br>Karlie Morgan<br>Signer Name: Karlie Morgan<br>Signing Reason: I approve this document<br>Signing Time: 07-Nov-2023 \| 14:32:06 GMT<br>F420CE2095794AFD8CD1DC3D32055809 |
| Global Clinical Strategy Franchise Head | Amir Kamali<br>Sr. Director, Global Clinical Strategy – Hips & Knees | DocuSigned by:<br>Amir Kamali<br>Signer Name: Amir Kamali<br>Signing Reason: I approve this document<br>Signing Time: 03-Nov-2023 \| 10:39:52 GMT<br>EC3CA19074E446478E070292EA2D4130 |
| Medical Affairs | Justin Templeton<br>Medical Director | DocuSigned by:<br>Signer Name: Justin Templeton<br>Signing Reason: I approve this document<br>Signing Time: 02-Nov-2023 \| 17:42:10 GMT<br>AA2E1C3040C348A39FB3C66B8DE9730A |
| Regulatory Representative | Samantha Staubach<br>Director, Regulatory Affairs, Orthopedics & Robotics | DocuSigned by:<br>Samantha Staubach<br>Signer Name: Samantha Staubach<br>Signing Reason: I approve this document<br>Signing Time: 10-Nov-2023 \| 01:23:58 GMT<br>F98C0312B79E465886DECAA76CD4B963 |

| Role | Job Title | DocuSign Stamp |
|---|---|---|
| Clinical Compliance and Training | Kate Drysdale, Sr. Clinical Compliance and Training Manger | DocuSigned by:<br>Kate Drysdale<br>Signer Name: Kate Drysdale<br>Signing Reason: I approve this document<br>Signing Time: 02-Nov-2023 \| 14:36:57 GMT<br>C3124B89DAB7491083D68451D2B9ED3C |

# 3 Protocol version history

**Table 3: Protocol version history**

| Protocol Version | Protocol Date | Summary of change |
|---|---|---|
| V1.0 through V3.0 are internal revisions and did not receive regulatory approvals | | |
| V4.0 | 08Apr2014 | Conditional approval |
| V5.0 | 08Apr2016 | Change to include cross-sectional imaging for subjects that experience dislocation, Metal ion blood draws to continue for subjects who become pregnant and removed ceramic head and femoral stem sizes that reflect commercially available in countries of study being conducted |
| V6.0 | 11Jan2018 | Contralateral hips allowed to be implanted in the study, clarifying when a study is enrolled into the study, removing the sample size re-estimation plan, and amending the device labeling. |
| V7.0 | 10Apr2020 | Change to include COVID-19 data and safety collection measures during the COVID-19 pandemic. |
| V8.0 | 06Oct2023 | Change to stop following the control arm and only follow the investigational study arm out to 10 years, update safety section, clarification on telehealth data collection and addition of flow charts for: increased metal ion levels, symptomatic hips, and imaging findings |

# 4 Signatures

## 4.1 Principal Investigator Signature Page

Each study site principal investigator will sign and return this page to Smith & Nephew and a copy will be retained at the investigational site.

☐ I have read the attached protocol entitled A Multi-Center, Randomized Controlled Study of Efficacy and Safety of the OXINIUM◊ DH Total Hip Replacement System in Subjects with Non-Inflammatory Arthritis version 8.0, dated 06/OCT/2023, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 12 of the protocol,

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith & Nephew.

| **Name, Address, Professional Position** | **Signature and Date / DocuSign Stamp** |
|---|---|
| | |

## 4.2 Coordinating Investigator Approval

Coordinating Investigator (CI) for the study will return this page to Smith & Nephew and a copy will be retained at the investigational site.

☐ I have read the attached protocol entitled A Multi-Center, Randomized Controlled Study of Efficacy and Safety of the OXINIUM◊ DH Total Hip Replacement System in Subjects with Non-Inflammatory Arthritis version 8.0, dated 06/OCT/2023, and agree to abide by all provisions set forth therein.

| **Name, Address, Professional Position** | **Signature and Date / DocuSign Stamp** |
|---|---|

# 5 Protocol Synopsis

**Table 4: Protocol Synopsis**

| | | |
|---|---|---|
| **Title of Study:** | A Multi-Center, Randomized Controlled Study of Efficacy and Safety of the OXINIUM◊ DH Total Hip Replacement System in Subjects With Non-Inflammatory Arthritis | |
| **Short Title** | OXINIUM◊ DH THA Pivotal Study | |
| **Study Type:** | Interventional | |
| **Sponsor** | Smith & Nephew, Inc.<br>1450 E. Brooks Road<br>Memphis, TN 38116 USA | |
| **Objective** | Ver 4.0 (first approved version), 08APR2014 | Ver. 8.0 (current version), 06OCT2023 |
| | The aim of this study is to demonstrate that the OXINIUM◊ DH Hip System is non-inferior to commercially available hip replacement device in Subjects with non-inflammatory degenerative joint disease. | The aim of this study is to monitor safety of the subjects implanted with the OXINIUM◊ DH Hip System up to 10-years post-implantation |
| **Study Hypothesis** | The primary hypothesis is that the proportion of Subjects classified as overall success in the Investigational Group treated with OXINIUM◊ DH Hip System will be non-inferior compared to proportion of Subjects classified as overall success in the Control Group treated with commercially available hip replacement device. | |
| **Indication** | Non-inflammatory degenerative hip joint disease (NIDJD) or any of its composite diagnoses such as osteoarthritis, avascular necrosis, traumatic arthritis, slipped capital epiphysis, fused hip, fracture of pelvis, and diastrophic variant. | |
| **Intervention** | Investigational Device: OXINIUM◊ DH Hip System (Smith & Nephew), Smith & Nephew R3◊ acetabular shell and ANTHOLOGY◊, SYNERGY◊ or collarless POLARSTEM◊ un-cemented femoral stem.<br><br>Control Device: BIOLOX◊ delta ceramic heads; R3◊ acetabular shell and XLPE liners; ANTHOLOGY◊, SYNERGY◊ or collarless POLARSTEM◊ un-cemented femoral stem. | |
| **Study Design** | Ver 4.0 (first approved version), 08APR2014 | Ver. 8.0 (current version), 06OCT2023 |
| | Interventional, randomized, controlled for efficacy and safety | Safety cohort |

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|---|---|---|
| **Primary Objective:** | Ver 4.0 (first approved version), 08APR2014 | Ver. 8.0 (current version), 06OCT2023 |
| | The primary endpoint in this study is a composite endpoint of overall success at 730 days post-operative in subjects with a unilateral hip implant. To be classified as overall success, the Subject must meet all of the following criteria:<br>• Clinical Success<br>  ○ Harris Hip Score of 80 or more at the 730-day follow-up time point.<br>• Radiologic success at the 730-day follow-up time point defined as:<br>  ○ No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, and<br>  ○ No femoral or acetabular subsidence greater than or equal to 5mm from baseline, and<br>  ○ No acetabular cup inclination changes greater than 4 degrees.<br>• Absence of Revision<br>  ○ No reoperations that led to removal or replacement of any of the acetabular or femoral components at the 730-day follow-up time point. | The primary objective of the study is to monitor the safety of the subjects enrolled in the investigational arm of the study up to 10-years post-surgery. |
| **Secondary Endpoints** | • Difference in Western Ontario and McMaster Universities Osteoarthritis Index v 3.0 (Likert) Functional Limitation Score between baseline (Admission) and the 730-day follow-up time point. The endpoint will be handled separately for unilateral and bilateral subjects. | |
| **Other Endpoints:** | • EQ-5D Health Utility Score<br>• Harris Hip Score<br>  ○ Total Score<br>  ○ Pain<br>  ○ Function<br>  ○ Absence of Deformity<br>  ○ Range of Motion<br>• Hip Disability and Osteoarthritis Outcome Scores v2.0 (HOOS)<br>  ○ Pain<br>  ○ Symptoms | |

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| | ○ Activities of Daily Living<br>○ Sport/Recreation<br>○ Quality of Life (QoL)<br>• WOMAC v3.0<br>○ Total Score<br>○ Pain<br>○ Stiffness<br>○ Functional Limitation<br>• Forgotten Joint Score-12 (FJS-12)<br>• UCLA Activity Score<br>• Subject Satisfaction with Outcome<br>• Hip Noise Evaluation Questionnaire<br>• Radiology outcomes<br>• Revision<br>• Metal ion concentration in whole blood<br><br>For the Control group, these will only be assessed through the 3-year follow-up time point. |
| **Safety evaluations** | • Adverse Events (AE) |
| **Length of Study:** | 730 days follow-up for primary analysis; minimum 3 years follow-up for all subjects, 10 years extended follow-up for Investigational subjects. The extended follow-up will run in two phases: Phase I will include clinic visits at year 3, 4 and 5. Phase II will include mailed questionnaires or phone follow-up at years 6, 7, 8, 9 and 10.<br><br>Upon approval of this protocol, subjects in the Control arm will be discontinued. Subjects in the investigational arm of the study will be followed until 10 years post-surgery. Clinic visits will be arranged for symptomatic subjects, if necessary. |
| **Number of Sites:** | 12 investigational sites in the US, 1 site in Canada and 2 sites in Australia |
| **Sample Size:** | 412 subjects (206 in the Investigational and 206 in the Control Group). |
| **Follow-up Schedule** | Screening, Admission, Surgery, Discharge, 42 days, 180 days, 365 days, 730 days, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, and 10 years. |
| **Statistical Planning** | The primary study hypothesis is that the proportion of Subjects classified as overall success in the Investigational Group treated with OXINIUM◊ DH Hip System will be non-inferior compared to proportion of Subjects classified as overall success in the Control Group treated with commercially available hip replacement device. The statistical null-hypothesis is that the proportion of Subjects classified as overall success in the Investigational Group at 730 days is inferior to the proportion of Subjects classified as overall success in the in the Control Group at 730 days. |

$$H_0: \pi_I - \pi_C \leq \delta;$$

$$H_a: \pi_I - \pi_C > \delta;$$

where,

$\pi_I$ is a population proportion of Subjects classified as overall success at 730 days among the Subjects treated with the Investigational Device; $\pi_C$ is a population proportion of Subjects classified as overall success at 730 days among the Subjects treated with the Control Device, and $\delta$ is the non-inferiority margin.

The non-inferiority margin $\delta$ is set to -.1 (-10%). Statistical definition of success is rejection of $H_0$. The null hypothesis will be tested by constructing a two-sided 95% confidence interval for the difference in proportions of Subjects classified as clinical success between the Investigational and the Control Group. If the lower boundary of such interval does not include $\delta$, the null hypothesis will be rejected, the study will reach a statistical criterion for success and, the primary study hypothesis will be confirmed.

For purposes of the primary study hypothesis, results will be presented separately for unilateral subjects and bilateral subjects. Unilateral subjects are defined as enrolled subjects who do not undergo a total hip replacement (THR) on the contralateral hip. Bilateral subjects are defined as enrolled subjects that undergo THR on the contralateral hip. Bilateral subjects will be further divided into 4 groups for analysis: subjects with the same implant in both hips (ODH/ODH or Control/Control) and subjects with different implants in both hips (ODH/Other or Control/Other). From a previous clinical study, it is estimated that approximately 10% subjects will require THR in the contralateral hip within 730 days of the first enrolled hip, thus the required sample size is inflated by this amount so as to preserve power in the unilateral subject analysis.

A secondary efficacy outcome of change in WOMAC 3.0 Functional Limitation score will be tested using a non-inferiority approach with a non-inferiority margin of -7.9 on a scale of from 0 (best) – 100 (worst). The hypothesis will be tested by one-sided t-test at the alpha level of 0.025. If the study reaches non-inferiority confirmation, data will be further evaluated for superiority.

Other outcomes will be evaluated using appropriate statistical methods and superiority approaches. For quantitative outcomes this will be based on two-way repeated measurements Analysis of Co-variance. Revision rates in the Investigational and the Control Groups will be evaluated using Log-rank test and Kaplan-Meier survival estimates.

Adverse events will be tabulated by time to occurrence and relationship to surgery and study device.

Randomization will be performed in the ratio 1:1 Investigational: Control Subject. The randomization sequence will be stratified by investigational site

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| | and will use random permuted blocks of size 2 and 4. Randomization will be organized by a centralized system and will be performed as close to the time of surgery as logistically possible. Subjects will be told about the randomized assignment after the surgery.<br><br>The primary efficacy analysis will be based on Per-protocol Population (PP). For this study the Per-protocol Population is defined as any Subject who receives the study device and does not have major protocol deviations. The secondary efficacy analysis will be performed on Intention-to-Treat (ITT) Population.<br><br>The safety analysis will be performed on Modified Intention-to-Treat Population which will include all randomized and enrolled Subjects from the investigation who were treated with an OXINIUM◊ DH Hip System who have at least one follow-up.<br><br>The sample size of 308 Subjects will have 80% power to reject the null hypothesis for the primary endpoint under the assumption of zero difference between the Investigational and Control Groups and proportion of clinical success outcome of .89. The actual sample size will be increased by 15% to accommodate for Subject attrition. In addition, the sample size will be increased by a further 10% to allow for subjects to undergo THR on the contralateral hip prior to the 730 days follow-up for the primary analysis, while preserving the required power for analysis of unilateral-only subjects.<br><br>Thus, the final sample size will include 412 Subjects (206 in the Investigational and 206 in the Control Groups). |
| **Staged Investigation** | The Sponsor will organize the study as a staged investigation. The available safety information for investigational and Control Subjects will be analyzed at the time when the last of the first 30 investigational Subjects reaches the 42-day follow-up time point. The enrollment of the additional Subjects will not discontinue at this stage. No efficacy data will be analyzed at this time. An additional analysis of the safety data will be performed when the last of the staged cohort Subjects reaches the 180-day follow-up time point. |

# 6 Background Information

Total hip arthroplasty (THA) is a common and successful surgical approach for treatment of severe osteoarthritis and other conditions that affect the hip joint. Various types of artificial hip joints are used in the procedure, using different materials for the bearing couple. Common bearing couple combinations are metal on polyethylene (MoP), metal-on-metal (MoM), ceramic-on-ceramic (CoC) and ceramic-on-polyethylene (CoP).

## 6.1 Investigational Device

The Investigational Device consists of two articular components, the OXINIUM◊ DH femoral head and the OXINIUM◊ DH acetabular liner, and the components listed in section 3.3.

OXINIUM◊ DH femoral heads and liners are made from an oxidized wrought Zirconium-2.5 Niobium alloy (ASTM F2384). An additional diffusion hardening process occurs after oxidation in the manufacture of OXINIUM◊ DH. During this additional process, part of the oxide substrate is dissolved and diffuses into the metallic substrate thereby increasing the thickness of the diffusion hardened zone beneath the oxide layer from 2-5 µm to 15-25 µm. The dissolution of the oxide to form diffusion hardened zone is controlled in such a way that the final oxide thickness of OXINIUM◊ DH meets the oxide thickness specification of OXINIUM◊ devices (thickness: 3.0 to 8.6 micron). This increased depth of hardening is intended to improve the damage resistance and allows for the material to be used in a hard-on-hard application.

The OXINIUM◊ DH femoral heads to be used as a component of the Investigational Device in this study are supplied in a range of 11 diameters and match to Smith & Nephew commercially available femoral stem components featuring a 12/14 locking taper either directly or with the use of a modular taper sleeve adapter. OXINIUM◊ DH femoral heads featuring either a 32mm or 36mm outer diameter and an internal 12/14 locking taper are offered in five (XS/-3, S/+0, M/+4, L/+8, XL/+12) offsets. OXINIUM◊ DH femoral heads featuring a 40mm outer diameter and an internal 12/14 locking taper are offered in four (XS/-4, S/+0, M/+4, XL/+8) offsets. All other OXINIUM◊ DH femoral head offerings (38-54mm outside diameter) require the use of a modular taper sleeve which will determine the final femoral head offset (XS/-4, S/+0, M/+4, L/+8).

The OXINIUM◊ DH Acetabular Liners are supplied in a range of 21 sizes and match to a specific size combination of R3◊ shell outside diameter and OXINIUM◊ DH femoral head diameter. Modular liner components mate with the R3◊ shells utilizing a taper-locking connection. The OXINIUM◊ DH acetabular liner utilizes the taper connection design as the R3◊ forte ceramic acetabular liner. Both liners interface with an R3◊ shell. OXINIUM◊ DH acetabular liners are not cleared or approved for use by the Food and Drug Administration (FDA).

The investigational OXINIUM◊ DH acetabular liners and femoral heads to be used in the current study are:

- Smith & Nephew OXINIUM◊ DH acetabular liners (sizes 32/46, 32/48, 32/50, 36/50, 36/52, 36/54, 36/56, 38/50, 40/52, 40/54, 40/56, 40/58, 40/60, 40/62, 42/54, 44/56, 46/58, 48/60, 50/62, 52/64 and 54/66-70 mm);

- Smith & Nephew OXINIUM◊ DH femoral heads (sizes 32, 36, 38, 40, 42, 44, 46, 48, 50, 52 and 54 mm).

The entire hip replacement system is comprised of OXINIUM◊ DH femoral modular head, OXINIUM◊ DH acetabular liner, compatible commercially available Smith & Nephew R3◊ acetabular metal shell and compatible commercially available Smith & Nephew femoral stems (ANTHOLOGY◊, SYNERGY◊ or collarless POLARSTEM◊). Acetabular threaded apex hole covers and, taper sleeve adapters (12/14 to 18/20) are also used with the system. Instrument sets are provided as standard with Smith and Nephew R3◊ acetabular shells and femoral stem systems. The femoral liner and head compatibility is provided in Instructions for Use.

Non-clinical testing has demonstrated that the OXINIUM DH Hip System is MR Conditional. A subject with this device can be safely scanned in an MR system meeting the conditions outlined in the Instructions for Use and in Appendix II.

### 6.1.1 Handling of the Investigational Device

Investigational Devices will have unique catalog numbers and will be labeled in accordance with 21 CFR 812. Only qualified Investigators participating in the study will receive investigational product. No investigational product will be released until an IRB/REB/EC/HREC has reviewed and approved the clinical study and until the use of the product is permitted by the FDA and the Sponsor.

Access to Investigational Devices shall be controlled, and the Investigational Devices shall be used only in the clinical investigation and according to the protocol. The device must be stored separately from any other inventory and accessible only to the Investigator or study designee(s).

Upon completion of study enrollment, the Investigator will return any remaining supply of the device according to the Sponsor's directions.

Record keeping requirements for Investigational Device inventory are described in Section 12.5.

## 6.2 Control Device

The Control Device is BIOLOX◊ delta ceramic head (32mm and 36mmdesigns in +0mm, +4mm and +8mm offsets), compatible commercially available Smith & Nephew R3◊ acetabular metal shell, XLPE liners, and compatible commercially available Smith & Nephew femoral stems (ANTHOLOGY◊, SYNERGY◊ or collarless POLARSTEM◊). Acetabular threaded apex hole covers and taper sleeve adapters (12/14 to 18/20) are also used with the system. Instrument sets are provided as standard with Smith & Nephew R3◊ acetabular shells and femoral stem systems.

Non-clinical testing has demonstrated that the Control Device is MR Conditional. A subject with this device can be safely scanned in an MR system meeting the conditions outlined in Appendix III.

## 6.3 Investigational Devices for this Study - Acetabular Shells, Taper Sleeves, Femoral Stems, and Hole Covers

Both the OXINIUM◊ DH and the Control Device are used in combination with previously cleared Smith & Nephew acetabular shells, taper sleeves, femoral stems, and hole covers.

The R3◊ Acetabular Shells are supplied in a range of twelve sizes ranging in outside diameter from 46 mm through 70 mm in 2 mm increments. Shells are supplied in 3 versions. (No screw holes, 3 screw holes, and multi-screw holes). The outer surface of each R3◊ acetabular shell contains an asymmetric porous beaded coating (STIKTITE◊). The mating OXINIUM◊ DH liner is assembled to the R3◊ acetabular shell through a taper locking mechanism. Each individual shell accommodates a specific OXINIUM◊ DH liner outside diameter size. Compatibility overview is provided in the Instructions for Use.

Smith & Nephew commercially available Titanium Modular adaptor sleeves are supplied with a range of 4 neck offsets (-4, +0, +4, +8). The taper sleeves feature an external 18/20 taper to assemble with sizes 38-54mm OXINIUM◊ DH femoral heads and a 12/14 internal taper to facilitate locking to Smith & Nephew femoral hip stems. Taper sleeves are not intended to be used with Smith & Nephew stems made of stainless steel alloys. Additional compatibility statements are provided in Instructions for Use.

Smith & Nephew commercially available ANTHOLOGY◊ cementless femoral stems are supplied in a range of twelve (Size 1 thru 12) sizes with standard and high neck offset. ANTHOLOGY◊ femoral stems are also offered with hydroxyapatite coating and uncoated for a total of 48 distinct femoral stem options. All stems feature a 12/14 locking taper and commercially pure titanium porous coating for biological fixation.

Smith & Nephew commercially available SYNERGY◊ cementless femoral stems are supplied in a range of ten (Size 9 thru 18) sizes with standard and high neck offset. SYNERGY◊ porous coated femoral stems are also offered both fully and partially coated with hydroxyapatite for a total of 60 distinct femoral stem options. All stems feature a 12/14 locking taper and commercially pure titanium porous coating for biological fixation.

Smith & Nephew commercially available collarless POLARSTEM◊ cementless femoral stems are supplied in a range of twelve (Size 126 mm thru 172 mm) standard stem sizes and eleven (Size 132 mm thru 172 mm) lateral stem sizes. Collarless POLARSTEM◊ femoral stems are offered with a Titanium and hydroxyapatite coating. All stems feature a 12/14 locking taper and commercially pure titanium coating for biological fixation.

Smith & Nephew commercially available Threaded Apex Hole Covers manufactured from a titanium alloy are offered in a single size and mate with the threaded apex hole of all R3◊ Acetabular Shells and apical peg of the OXINIUM◊ DH acetabular liner.

## 6.4 Regulatory Status

The OXINIUM◊ DH Hip System has not received pre-market approval from the FDA. The initial purpose of this Investigational Device Exemption (IDE) study was to support the Sponsor's PMA application. The

Sponsor is no longer seeking a PMA for the OXINIUM DH Hip System at the time of this Protocol Amendment, however data collected as part of this study may be used as an input for future research.

The OXINIUM◊ DH Hip System has not received approval for marketing by Health Canada. A clinical study application to use unapproved device has been submitted and approved by Health Canada. The study in Canada has commenced.

The device is not approved for marketing in Australia. The medical device study approval was obtained under the Clinical Trial Notification scheme (CTN) prior to initiating the study in Australia. The study has commenced in Australia.

### 6.5 Intended Use of the Device

The Smith & Nephew OXINIUM◊ DH Hip System is indicated for individuals undergoing primary surgery where other treatments have failed in rehabilitating hips damaged as a result of non-inflammatory degenerative joint disease (NIDJD) or any of its composite diagnoses such as osteoarthritis, avascular necrosis, traumatic arthritis, slipped capital epiphysis, fused hip, fracture of the pelvis, and diastrophic variant.

### 6.6 Justification for the Study

Original study was justified based on:

- Limitations in current hard-on-soft and hard-on-hard couplings and possibilities that OXINIUM◊ DH may overcome some of those limitations;
- Significant public health impact of noninflammatory degenerative hip joint disease;
- The operational technique remains per standard of care;
- Efficacy and safety of THA using the OXINIUM◊ DH Hip System has not been established.

The justification for the current study is the need to continue monitoring the safety of the subjects treated with the investigational device.

## 7 Risk Analysis

A number of risks for potential complications or adverse events are associated with total hip replacement. Many of these are risks associated with total hip replacement surgery, risk of general anesthesia and risk of post-surgical complications. Others are specific risks associated with the Subject participation in this study.

### 7.1 Anticipated risks

Anticipated AEs which may occur as a direct result of the treatment or general anesthesia are listed below. These risks will be present regardless of the participation in the study.

Hip surgery, like any medical procedure, carries risks. The risks of surgery include:

- A reaction to the anesthesia
- Heart attack
- Wound infection

- Excessive bleeding
- Blood clots

There may be adverse events after surgery, regardless of the type of hip system implanted including:

- Osteolysis or other bony abnormalities (including ectopic or heterotopic bone formation) as a result of wear, debris generation, or other causes;
- Failure to observe the Warnings and Precautions, trauma, strenuous activity, implant alignment, patient non-compliance, involuntary muscular disorders, improper use or duration of service increase the risk of loosening, bending, cracking, or failure of implant components, which may lead to revision surgery;
- Worsened pain, function, range of motion, or change in leg length;
- Fracture of the acetabulum, pelvic bones, or femur;
- Difficulty implanting prosthesis components;
- Superficial or deep wound infection occurring early or late;
- Nerve injury resulting in transient or permanent motor and/or sensory deficits;
- Wound hematoma and thromboembolic disease;
- Periarticular calcification disorders;
- Trochanteric nonunion (when a transtrochanteric surgical approach is used);
- Allergic reaction to materials;
- Large blood vessel damage and possible large blood loss (> 1500 ml) necessitating transfusion;
- Traumatic arthrosis of the hip from intraoperative positioning of the extremity;
- Delayed wound healing;
- Ipsilateral or contralateral limb problems due to leg length discrepancy, improper femoral alignment, or muscle deficiency;
- Temporary or permanent device related noise such as clicking or squeaking;
- Metal sensitivity reactions or other allergic/histological reactions to implant material;
- Hip dislocation.

## 7.2 Study related risks

Possible risks that may occur as a result of treatment with the OXINIUM◊ DH Hip System:

- Higher than normal wear of the OXINIUM◊ DH material may result in increased metal ion levels. Increased metal ion levels may lead to the need for revision of the implant.
- Exposure of the underlying metal surface which could lead to an increase in wear of the OXINIUM◊ DH material.
- The risk of organ toxicity due to accumulation of metal ions has not been determined in humans.
- Allergic reaction to the OXINIUM◊ DH material
- Temporary or permanent device related noise such as clicking or squeaking
- Pseudotumor formation
- Adverse reaction to metal debris

Risks that may occur as a result of study research procedures:

- Radiologic exposure
- Pain and bruising and possible infection at the site of blood draw and fainting

- Loss of confidentiality

## 7.3 Manner taken to minimize risks

The coupling portion of the Investigational Device is made of Zirconium and Niobium. Other elements are trace. There are no known adverse health effects of exposure to Zirconium and Niobium. Pregnant women should avoid exposure to increased levels of metal ions. Pregnancy and planned pregnancy is an exclusion criterion for this study. In order to collect data about possible risks associated with metal ion release blood metal ion levels will be measured for all Investigational and Control Subjects at the Admission time point. Any Subject that has a symptomatic study hip (defined below) during the follow-up period will have additional blood metal ion levels tested and radiographs at the time such event occurs and at each subsequent clinic follow-up visit or until the subject is no longer enrolled into the study **(Fig 2)**. Additional blood samples for metal ion analysis may be obtained between clinic visits as needed, as determined by the Investigator.

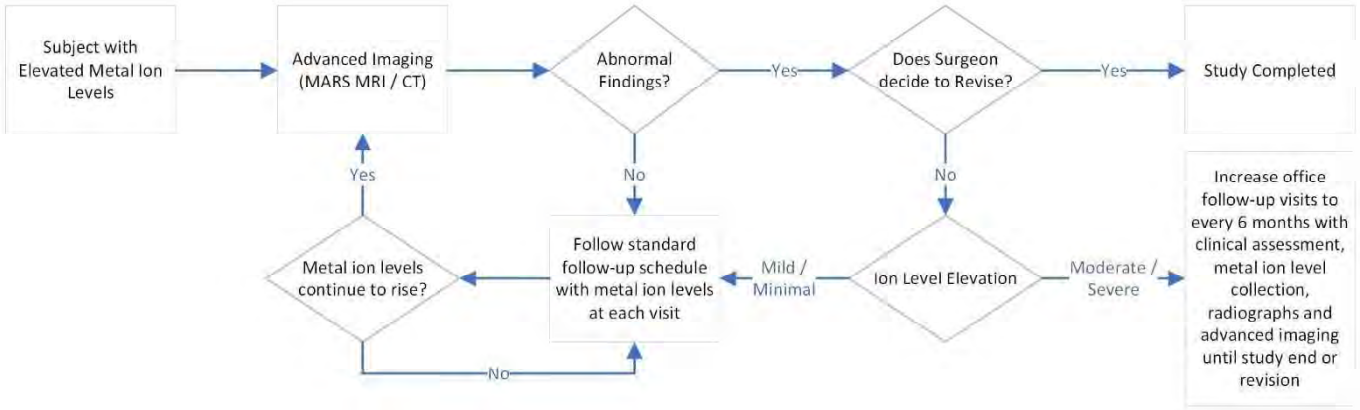
Subjects with elevated metal ion levels higher than 7ppb (parts per billion)* in Co (cobalt), Cr (chromium), Zr (Zirconium), Nb (Niobium), Ni (nickel)and Ti (titanium) will have advanced cross-sectional imaging performed **(Fig. 1)**. If there are no abnormal findings, the subject will continue with the normal follow-up schedule with metal ion levels collected at each subsequent visit. Cross-sectional imaging will be repeated only if metal ion levels continue to increase or there were abnormal findings during the previous imaging. If abnormal findings are present on the cross-sectional imaging, it will be the surgeon's decision whether to revise the subject. If the symptoms are mild and minimally elevated ion levels, and the surgeon decides not to revise the subject, the subject will continue with normal follow-up schedule with cross-sectional imaging and metal ion levels collected at each subsequent visit. If the metal ion levels are moderately or severely elevated and the surgeon decides not to revise the subject, the subject will return every 6 months for an in-person office visit for assessment by the principal investigator, blood collection for metal ion evaluation, radiographs and advance imaging at the discretion of the principal investigator.

*MHRA Guidelines. It has also been observed in both the control group and the ODH investigation arm that patients metal ions in Al (aluminium) are high or higher than the MHRA guidelines at pre-op, which could be linked to exposure to metal ions through water and food[1,2]. Therefore, the recommended threshold for Al metal ion levels is 15.1 ug/L (ppb)*, the upper reference limit set in the blood ion group of this study.

*Recommended threshold for Al metal ion levels is 15.1 ug/L (ppb)*

Ref 1. Rodushkin I et al., J. Food Compost. Anal. 24 (2011) 70–78.
Ref 2. Rodushkin I et al., Sci. Total. Environ. 392(2008),290-304.

**Figure 1: Elevated metal ion levels treatment algorithm**



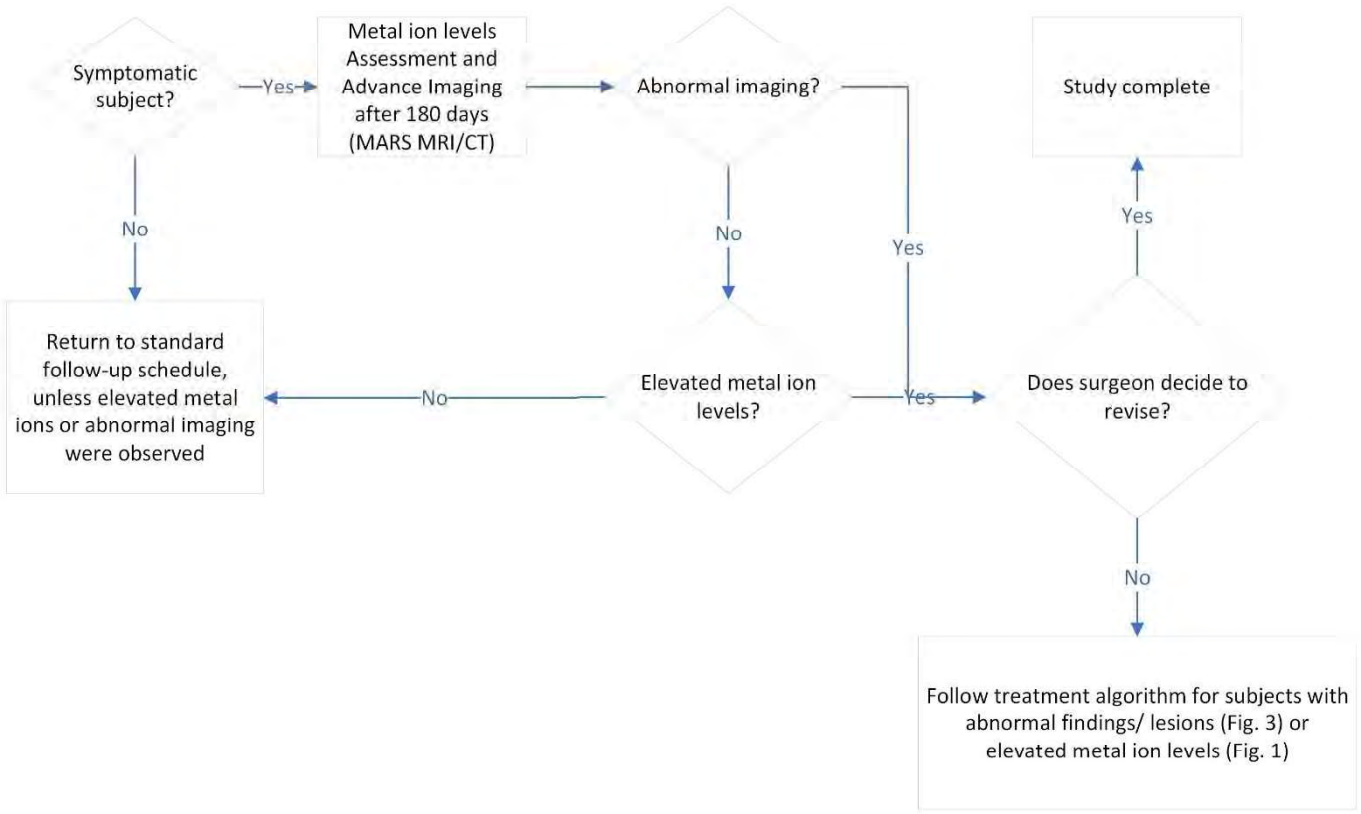

A symptomatic study hip is defined as one or more of the following present at the 180 day or later visit:

- Dislocation
- Unanticipated pain
- Clinically reproducible squeaking noise
- Clinically reproducible catching or locking of the hip
- Unanticipated swelling around the hip
- Requiring revision of the device

Unanticipated pain requiring additional metal ion analysis and radiographs is defined as moderate to severe hip or thigh pain reported as present at the 180-day follow-up time point or later that can otherwise not be explained by another adverse event or alternate diagnosis. Unanticipated swelling requiring additional metal ion analysis and radiographs is defined as moderate to severe swelling reported as present at the 180-day follow-up time point or later that cannot otherwise be explained by another adverse event or alternate diagnosis.

Device related noise (clicking and squeaking) is not an unknown phenomenon in total hip replacement. Devices that seem to be most affected are ceramic-on-ceramic couplings. In a series of Subjects who were actively asked about squeaking, the reported incidence varied from 11% (Schroder et al., 2011) to as high as 24.6% (Owen DH et al., 2014 B). In vast majority (97%) of cases, squeaking is not associated with clinical symptoms or other complaints. The reported incidence of revision due to squeaking ranges from 0.20% (Owen DH et al., 2014) to 0.26% (Stanat et al., 2012). In order to manage this risk data will be collected prospectively about noise associated with the artificial hip device.

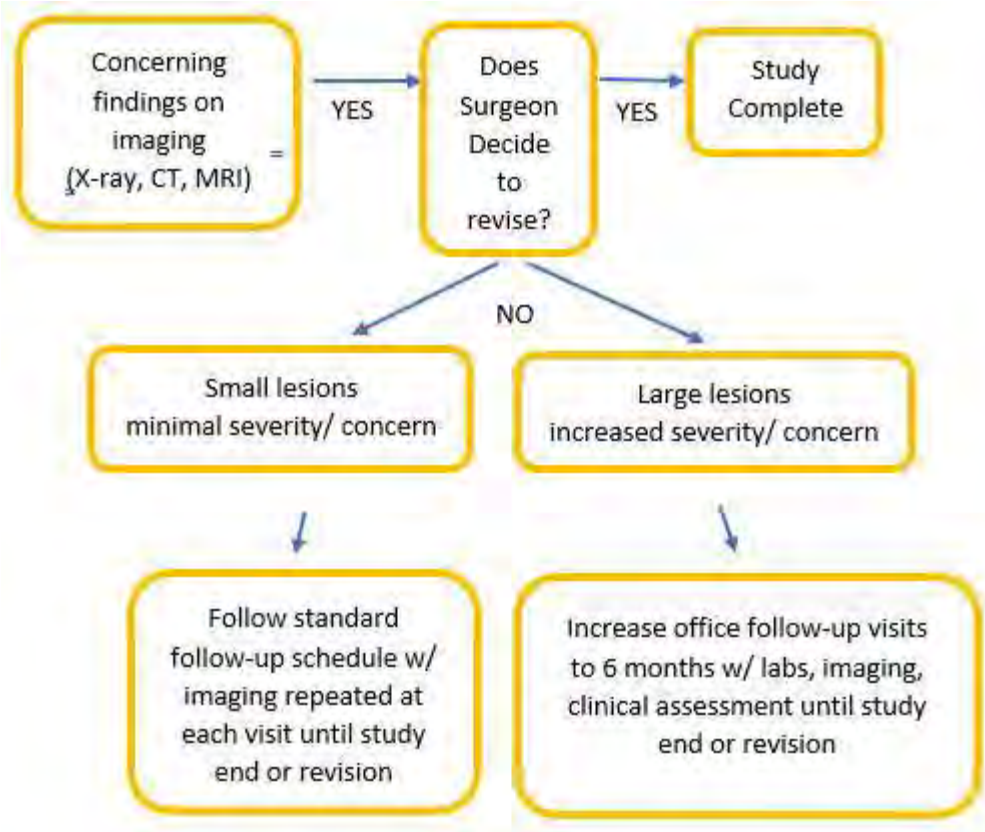
**Figure 2: Symptomatic subjects follow-up**




Pseudotumor formation has been described in some cases of metal-on-metal prostheses. Risk of pseudotumor formation for the Investigational Device is unknown. Monitoring of pseudotumor formation will be conducted using study procedures for AE capture, through regular clinical monitoring of Subject progress, radiologic imaging, and metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI). MARS MRI will be indicated for study Subjects at the 180-day follow-up time point or later who are symptomatic according to the definition above. Computed tomography (CT) may be used in place of MARS MRI of monitoring of pseudotumor formation only if the subject is contraindicated for MRI.

It remains at the discretion of the surgeon when device removal/revision should occur. In the case of pseudotumor formation or other concerning findings on MRI or CT, it is recommended that the subject be followed every 6 months or more frequent with an in-office visit for repeat imaging, clinical assessment and evaluation of revision/removal **(Fig 3)**.

**Figure 3: Abnormal imaging findings treatment algorithm**




Some radiologic evaluations used in this study may not be considered standard of care. Study-related additional radiologic exposure does not pose significant general health risk due to use of plain radiographs associated with low radiation dose. The benefit of monitoring symptomatic study hips with MARS MRI or CT outweighs the additional radiologic exposure. Pregnant women should not receive radiologic-assessments. Pregnancy and planned pregnancy is an exclusion criterion for the study. If a Subject becomes pregnant during the course of this study, the Subject will not participate in radiographic study assessments including plain radiographs, MARS MRI, and CT. Other study assessments and evaluations will continue according to the assessment schedule including blood draws for metal ion assessment. The Subject will resume radiographic assessments once pregnancy has ended. If the Subject consents, the Subject may be followed to obtain information about the pregnancy and outcome of the pregnancy.

Risk of pain, bruising, possible infection at the site of blood draw, and fainting will be reduced by use of approved medical equipment for blood draws and personnel trained in phlebotomy. The sample size and frequency of blood draws for ion analysis will be kept to baseline testing for all Subjects, additional ion testing as required for symptomatic study hips, and a 70 Subject cohort that will receive five blood draws at pre-defined time points.

The risk of loss of privacy will be mitigated by following Good Clinical Practice (GCP) compliant procedures to manage Subject confidentiality and study operations. Subjects will be identified by the

assigned Subject number on Case Report Forms (CRFs) and other documents submitted to the Sponsor. Documents that will not be submitted to the Sponsor and that identify the Subject (e.g., the signed informed consent form) will be maintained in strict confidence by the site Investigator, except to the extent necessary to allow auditing by the appropriate ethics authority and the study monitor.

All serious adverse events will be reviewed on an ongoing basis by the internal cross-functional team. Sponsor will review all adverse events to identify unexpected device related adverse events. Further details about adverse events monitoring is provided elsewhere in this document.

# 8 Study Design

## 8.1 General Overview

This is a prospective, multi-center, interventional, randomized controlled study to investigate the safety and efficacy of the OXINIUM◊ DH Hip System (Smith & Nephew, Inc., Memphis, TN, USA). The study will follow enrolled Subjects for 730 days for the primary endpoint analysis and Investigational subjects for 10 years (extended follow-up) in total. Upon approval of Protocol (v8.0) by the FDA and IRB, all subjects randomized to the Control cohort will be notified that their participation in this clinical study has been concluded and no further study related exams will be performed, or data collected. The study will then follow a safety cohort design. Subjects meeting inclusion and exclusion criteria will receive THA and will be randomized to receive implantation of the Investigational or Control Device. The post-operative rehabilitation will be per standard of care at the treating institution. Up to 12 US and 3 out-of-US (OUS) enrolling investigational sites will participate in this study.

## 8.2 Study Objectives

The primary objective of this study is to demonstrate that the OXINIUM◊ DH Hip System is non-inferior to a commercially available hip replacement device in unilateral Subjects with non-inflammatory degenerative joint disease in terms of overall success.

Secondary objective is to demonstrate that OXINIUM◊ DH Hip System is non-inferior to commercially available hip devices in functional outcomes in both unilateral and bilateral subjects.

Upon approval of Protocol (v8.0), the objective of this study will be to monitor safety of the subjects implanted with the OXINIUM◊ DH Hip System up to 10-years post-implantation.

## 8.3 Hypothesis

The primary hypothesis is that the proportion of unilateral Subjects classified as overall success at the 730-day follow-up time point in the Investigational Group treated with OXINIUM◊ DH Hip System will be non-inferior compared to proportion of unilateral Subjects classified as overall success in the Control Group treated with commercially available hip replacement device.

## 8.4 Staged Enrollment

The study is designed as a staged investigation according to FDA Draft Guidance for Industry, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff (FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations from June 14, 2013; Section 5 Staged Approval or Staged Approval with Conditions). The available safety information will be analyzed on two occasions, when the last of the first 30 investigational Subjects reaches the 42-day (6 week) follow-up time point and when the last of the first 30 investigational Subjects reaches the 180-day (6 months) follow-up time point. At that time safety data will be also available for about 30 control subjects. The enrollment of the additional IDE Subjects will not discontinue due to staged analyses. No efficacy data will be analyzed for the Subjects at this time. The safety reports will be submitted to the FDA 42 days after the last Subject from the staged enrollment cohort reaches the 42 day and 180-day follow-up time points, respectively.

## 8.5 Investigational / Control Groups

Investigational Group Subjects will receive OXINIUM◊ DH Investigational Device in combination with FDA cleared components that include acetabular shells, taper sleeves, femoral stems and hole covers. Specifically, the Investigational Group Subjects will receive:

- OXINIUM◊ DH Investigational components,
- Smith & Nephew R3◊ acetabular shell,
- Smith & Nephew Titanium Modular adaptor,
- Smith & Nephew ANTHOLOGY◊, SYNERGY◊ or collarless POLARSTEM◊ un-cemented femoral stem and
- Smith & Nephew Threaded Apex Hole Covers.

Control Group Subjects will receive devices cleared for marketing:

- BIOLOX◊ delta ceramic heads,
- Smith & Nephew XLPE liners,
- Smith and Nephew R3◊ acetabular shell,
- Smith & Nephew Titanium Modular adaptor,
- Smith & Nephew ANTHOLOGY◊, SYNERGY◊ or collarless POLARSTEM◊ un-cemented femoral stem and
- Smith & Nephew Threaded Apex Hole Covers.

## 8.6 Endpoints

### 8.6.1 Primary Endpoint

The primary endpoint in this study is a composite endpoint of overall success at 730 days post-operative in unilateral subjects. To be classified as overall success, the unilateral Subject must meet all of the following criteria:

Clinical success:

HHS of 80 or more at the 730-day follow-up time point.

Radiologic success at the 730-day follow-up time point 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 5mm from baseline;

No acetabular cup inclination changes greater than 4 degrees.

Absence of revision at the 730-day follow-up time point:

No reoperations that led to removal or replacement of any of the acetabular or femoral components.

The Harris Hip Score is a clinician-based 10 item questionnaire used to evaluate the results of hip surgery. It is comprised of four subsections yielding a maximum possible score of 100 points collectively, including Pain (44 points), Function (47 points), Absence of Deformity (4 points) and Range of Motion (5 points). The total score has 100 points, ranging from 0 (poor) to 100 (best).

Radiologic success in regard to radiolucencies can also be defined as no radiolucencies greater than 2 mm in 2-3 of the 3 acetabular zones and 4-7 of the 7 femoral zones in both AP and lateral views. Radiologic evaluations are described in Section 8.6.3.

Any reoperation in which the entire or part of the device system has been removed or replaced will be defined as a revision.

The primary objective after the 730-day follow-up time point is to monitor the safety of the subjects enrolled in the investigational arm of the study up to 10-years post-surgery.

### 8.6.2 Secondary Endpoint

The secondary endpoint is the difference in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) version 3.0 Likert Scale Functional Limitations Score between baseline (Admission) and the 730-day post-operative time point. The endpoint will be handled separately for unilateral and bilateral subjects.

The WOMAC is a 24 item subject-reported self-assessment questionnaire. It evaluates pain (5 questions), stiffness (2 questions), and functional limitation (17 questions) in knee and hip osteoarthritis. In this study version 3.0 of the instrument is used, which employs a 5-point Likert scale (ranging from none (0) to extreme (4)). The Functional Limitations Score takes values from 0 (no problems) to 68 (extreme problems). In this study, the scale will be transferred into 0 (best) to 100 (worst). The WOMAC version 3.0 Likert Scale questionnaire which can be derived from the Hip Disability and Osteoarthritis Outcome Scores version 2.0 will be used.

### 8.6.3 Other Endpoints

Other endpoints included in the study are listed below, which will be handled separately for unilateral and bilateral subjects. For the Control group, these will only be assessed through the 3-year follow-up time point.

EQ-5D Health Utility Score

Harris Hip Score

Total Score

Pain

Function

Absence of Deformity

Range of Motion

Hip Disability and Osteoarthritis Outcome Scores v2.0 (HOOS)

Pain

Symptoms

Activities of Daily Living

Sport/Recreation

Quality of Life (QoL)

WOMAC version 3.0

Total Score

Pain

Stiffness

Functional Limitation

Forgotten Joint Score-12 (FJS-12)

UCLA Activity Score

Subject Satisfaction with Outcome

Hip Noise Evaluation Questionnaire

Radiology outcomes

Revision

Metal ion concentration in whole blood

EQ-5D. The EuroQoL group has developed a standardized instrument EQ-5D for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it contains 5 questions (Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) and provides a simple descriptive profile and a single index value for health status preference. In addition, there is a Visual Analog Scale (VAS) question of health. The EQ-5D is designed for self-completion by Subjects and is ideally suited for use in mailed surveys, in clinics and face-to-face interviews. It is cognitively simple,

taking only a few minutes to complete. Instructions to Subjects are included in the questionnaire. Currently, there are three versions of the questionnaire, EQ-5D-3L; EQ-5D-5L and, EQ5D-Y. In this study the EQ-5D-3L version will be used.

HOOS. The Hip Disability and Osteoarthritis Outcome Score (HOOS) is developed as an instrument to assess the Subjects' opinion about their hip and associated problems. HOOS consists of 5 subscales; Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and hip related Quality of Life (QOL). The Subject is asked to take experience of last week into consideration when answering the questions. Standardized answer options are given (5 Likert boxes) and each question gets a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

Forgotten Joint Score. The Forgotten Joint Score (FJS-12) is a recently developed measure of the Subject's ability to forget the artificial joint in everyday life (Behrend H et al., 2012).

UCLA Activity Score. UCLA Activity Score is a measure of physical activity levels in Subjects undergoing total joint arthroplasty (Zahiri CA et al., 1998).

Subject Satisfaction. Subject Satisfaction with Outcome will be evaluated using a four-point ordinal scale from 'Very Satisfied' (4); Somewhat Satisfied (3); Somewhat Dissatisfied (2); to 'Very Dissatisfied' (1). Subject Satisfaction with Surgery will be evaluated asking if the Subject would undergo the same surgery with possible answers of 'Yes' and 'No'.

Hip Noise Assessment Questionnaires. Subject and clinician reports of hip noise will be evaluated using modified questionnaires developed by Schroder D et al., (2011).

Radiology Evaluations. This study requires anteroposterior (AP)-pelvis, AP-hip, and lateral (frog-leg or Lauenstein position) views obtained in the supine position on all Subjects shortly after implantation (baseline) and through 5 years post implantation. Radiographs will be obtained pre-operatively as well as at the Discharge, 42 Day, 180 Day, 365 Day, 730 Day, 3 Year, 4 Year, and 5 Year follow up time points. Additional radiographs will be obtained if the Subject presents with a symptomatic study hip as described in Section 4.3. The discharge images will be designated as the baseline radiographs for comparison with subsequent images. Radiograph reviews will be conducted by an independent radiologist. No blinding of the radiologist will be performed.

### 8.6.4 Metal Ion Analysis

Metal ions will be measured in whole blood drawn for all Subjects at the Admission time point.

Additional metal ion measurements will be performed as required for symptomatic study hips as described in Section 7.3. Metal ion measurements will be performed at each subsequent follow-up clinic visit if the symptom is ongoing. Subjects requiring revision surgery of the Investigational Device will also have blood collected prior to revision surgery for metal ion analysis.

Metal ion measurement will also be performed in all bilateral subjects as described in Appendix I.

Blood samples will be analyzed by a central laboratory. A laboratory manual will be provided to all sites. The following metal ion analyses will be performed: Al, Co, Cr, Mo, Nb, Ni, Ti, V, and Zr. The selected central lab(s) will be ISO-15189 certified. Ions will be measured through high resolution sector field inductively coupled plasma mass spectrometry (HR-SF-ICP-MS).

Date of blood draw will be reported.

### 8.6.5 Cross-sectional Imaging

MARS MRI will be indicated for subjects who present with a symptomatic study hip as described in Section 7.3 at the 180 Day follow-up time point or later. Subsequent MARS MRI assessments will be performed at each follow-up clinic visit if the subject continues to be symptomatic according to the definition or if there is a finding in the previous image review. CT may be used in place of MARS MRI only if the subject is contraindicated for MRI. Cross-sectional images will be evaluated for fluid formation, synovial characteristics, and involvement of surrounding tissue. In addition, any lesions found on MARS MRI scans will be categorized according to the classification system by AJ Hart et al. (2012). All cross-sectional image reviews will be conducted by an independent radiologist.

### 8.6.6 Safety Evaluations

Incidence of AEs will be summarized by time to occurrence and relationship to surgery and device. All AEs through the 3-year follow-up time point will be listed, and all AEs from the Investigational (OXINIUM◊ DH Hip System) will be listed through the 10-year follow-up time point. Trends in Adverse Events (AEs), Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs), and Unanticipated Adverse Device Effects (UADEs) will be periodically evaluated as described in Section 10. Collection, evaluation and reporting of AEs are described in Section 11.

## 8.7 Surgical Technique

Implantation of the Investigational Device is performed per standard surgical procedure for THA, as described in the Instructions for Use. The Control hip system will be implanted in accordance with the R3◊ Instructions for Use that are also standard surgical approach in THA. SYNERGY◊, ANTHOLOGY◊ and collarless POLARSTEM◊ femoral components will be implanted per their respective standard of care surgical techniques. Surgical technique brochures for the implantation of all components included in this study will be provided to each site.

## 8.8 Surgical Training

Surgeons selected to participate in this study as Investigators will be licensed orthopedic surgeons with documented experience in performing THA. Surgical techniques and approaches used in this study are standard of care. Device implantation training will be provided by the Sponsor.

## 8.9 Inclusion Criteria

- Age between 22 and 79 years, inclusive;
- Subject is skeletally mature in Investigator's judgment;

- Subject has a non-inflammatory degenerative joint disease (NIDJD) or any of its composite diagnoses such as osteoarthritis, avascular necrosis, traumatic arthritis, slipped capital epiphysis, fused hip, fracture of the pelvis, and diastrophic variant requiring unilateral primary total hip replacement;
- Preoperative (within 28 days prior to the surgery) total Harris Hip Score of less than 70;
- Subject is a suitable candidate for primary total hip replacement at the discretion of the investigator;
- Subject has given consent to participate in the study after the nature, scope, and possible consequences of the study have been explained in an understandable form;
- Subject is willing and able to participate in required follow-up visits at the investigational site and to complete study procedures and questionnaires.

## 8.10 Exclusion Criteria

- Subject has had a previous total hip replacement, hemi-arthroplasty, or fusion in either Hip (NOTE: will not apply if contralateral hip is implanted, see Section 8.11);
- Subjects who, in the opinion of the Investigator, will possibly require a separate joint replacement operation within the next two years, including revision operations in the other (not study) hip (NOTE: will not apply if contralateral hip is implanted, see Section 8.11);
- Subject has a known allergy to any component of the devices used in the study;
- Subject with an insufficient acetabular or femoral bone stock in which good anchorage of the implants are unlikely or impossible;
- Subject with total or partial absence of the muscular or ligamentous apparatus of the hip joint to be operated;
- Subject has a congenital disorder or deformity of the affected limb or significant anatomic variance of the affected hip (based on Investigator's discretion);
- Subject has an active malignancy or history of invasive malignancy within the last five years, with the exception of superficial basal cell carcinoma or squamous cell carcinoma of the skin that has been definitively treated. Subjects with carcinoma in situ of the uterine cervix definitively treated more than 1 year prior to enrollment may enter the study;
- Subject has rheumatoid arthritis;
- Subject has a Body Mass Index > 40;
- Subject has an active infection (e.g. hepatitis, Acquired Immunodeficiency Syndrome, AIDS related Complex) - systemic or at the site of intended surgery;
- Subject has contralateral lower extremity condition causing abnormal ambulation and noncompliance with rehabilitation;
- Prior proximal femur fracture and/or presence of malunion, nonunion, on the surgical side;
- Subject has conditions that may interfere with THA survival or outcome (e.g., Paget's disease, Charcot's disease, vascular insufficiency, muscular atrophy, uncontrolled diabetes defined by HgbA1c > 7%, or neuromuscular disease);
- Subject has systemic steroid therapy with 1 month prior to surgery;

- Subject is on drug therapy for the index hip with intra-articular corticosteroid therapy or any intra-articular therapy within 3 months of enrollment into the study;
- Subject has a life expectancy less than 10 years;
- Subject is female and of child bearing age who is currently pregnant or not using contraception;
- Subject has known moderate to severe renal insufficiency;
- Subject has an emotional or neurological condition that would pre-empt their ability or willingness to participate in the study including mental illness, mental retardation, drug or alcohol abuse;
- Subject is entered in another investigational drug, biologic, or device study within 30 days of active study participation;
- Subject is unable, unwilling, or in the Investigator's opinion unlikely to return for or participate in follow-up visits at the investigational site;
- Subject is facing current or impending incarceration.

## 8.11 Bilateral Hip Implants

Subjects enrolled in the study for the first time will have 1 THA per inclusion/exclusion criteria and the randomization assignment. Subjects may require the contralateral hip to be replaced during study participation.

In consultation with the Investigator, subjects may have the contralateral hip replaced with the same hip system as originally assigned (without requirement for a separate randomization process to be followed) within 2 years of the first enrolled hip surgery date. Subjects randomized to Oxinium DH in the first enrolled hip may have an Oxinium DH hip implanted in the contralateral hip while subjects randomized to Biolox in the first enrolled hip may have Biolox implanted in the contralateral hip. Alternatively, the subject and investigator may choose to implant a different marketed hip system on the contralateral hip. In either case, exclusion criteria 1&2 will not apply, but all other inclusion/exclusion criteria must be met.

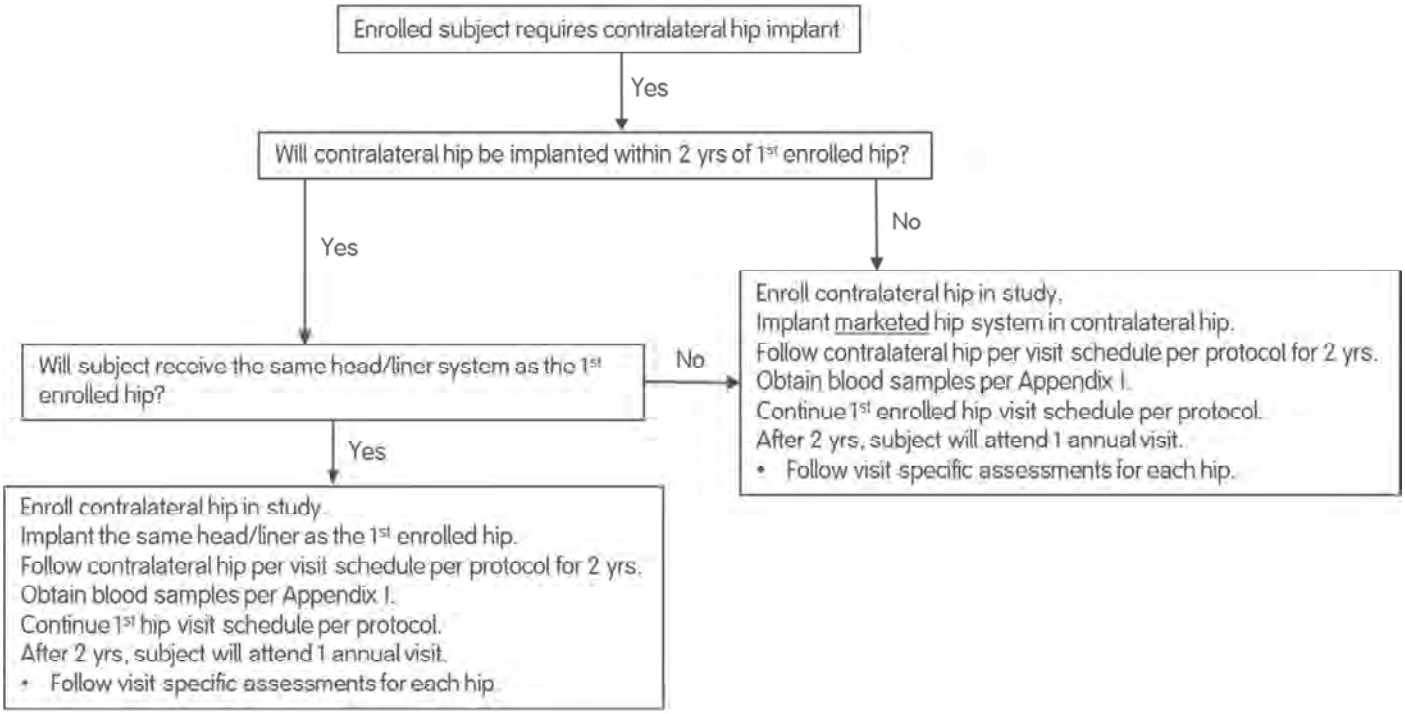
If a subject requires the contralateral hip implant more than 2 years after the date of the first enrolled hip implant, then the subject must be given a marketed hip system.

Subjects who receive a contralateral THR will follow the Visit schedule (see Table 6 and Sections 8.12.8.1 through 8.12.8.5) and procedures through the 2-year visit for the contralateral hip. Thus, these subjects will have separate visit schedules for each hip for 2 years. After the 2-year visit for the contralateral hip, subjects should follow the annual visit schedule for the first enrolled hip. Thus, from Year 2 forward for the contralateral hip, subjects will only be required to have 1 annual visit to examine both hips and obtain blood samples (see Appendix I). A protocol deviation will not be collected for an out of window visit when the visit schedule for the contralateral hip is aligned with the first enrolled hip.

The procedures to be completed at these annual visits will follow the visit schedule for each hip. For example, a subject reaches the 6-year visit for the first hip and is only required to have data collected via phone or mail, but the contralateral hip reached year 4. In this example, the subject would be required to visit the research office, have the year 4 procedures completed on the contralateral hip and also complete the questions for year 6 on the first enrolled hip.

When the 10-year visit for the first enrolled hip is complete, then the **subject** will be exited from the study. The contralateral hip will also be exited from the study, regardless of the number of visits completed for the contralateral hip.

**Figure 4: Enrollment of Contralateral Hip**




## 8.12 Study Procedures

Subject reported outcomes should be completed prior to physician assessments for all applicable study visits.

### 8.12.1 Pre-screening

Subjects receiving care at the investigative sites will be pre-screened as potential Subjects for the study. 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.

### 8.12.2 Screening

Subjects considered potential candidates for the study based on pre-screening must sign an IRB/REB/EC/HREC approved Informed Consent (IC) document prior to participating in any study activities and prior to being screened for this study. Once a Subject has completed the informed consent procedure and signed the Informed Consent document, the Investigator or delegated study research staff

can complete the screening process with the Subject. All potential Subjects who undergo the screening process will be documented on a Screening and Enrollment Log.

### 8.12.3 Blinding

There is no blinding involved. Subjects can be advised about treatment allocation after the surgery.

### 8.12.4 Randomization

For the first hip, the randomization will be performed as close to the time of surgery as logistically feasible. The randomization will be provided by a central randomization system. The randomization will be recorded in the Randomization Log to be stored in the Investigational Site's files. For subjects that require the contralateral hip to be replaced during study participation, a second randomization is not required; the contralateral hip is assigned the same hip system as the first hip enrolled for the subject.

### 8.12.5 Enrollment

Every Subject that is consented, screened, randomized and has the Investigational or Control device implanted during surgery will be considered Enrolled into the study. Subjects that are consented but do not meet the definition of Enrolled will be considered screen failures.

### 8.12.6 Device Replacement During the Surgery

If, for any reason, the Subject cannot receive the assigned device during the surgery, the study device will be replaced with a commercially available product of the Investigator's choosing. The reason(s) why the assigned study device was not used will be recorded in the appropriate CRF. Subjects who receive the non-assigned device will be considered a Screen Failure and will not be followed, but the data about the reason for non-use of the assigned device will be recorded.

### 8.12.7 Discharge

On the day of discharge, the site will collect discharge information, review concomitant medications, AEs/SAEs, collect discharge radiology images, and record any rehabilitation therapy assigned at the time of discharge.

### 8.12.8 Follow-up Evaluations

All follow-up schedules are based on "Day 0," which is the day of the surgery. Follow-up windows are shown in Table 5. Subjects will be evaluated according to the schedule set forth in Table 6.

**Table 5: Follow-up windows**

| **Follow up** | Window | Days (inclusive) |
|---|---|---|
| **Surgery** | N/A | 0 |
| **42 days** | ±7 days | 35—49 days |
| **180 days** | ±30 days | 150—210 days |
| **365 days** | ±60 days | 305—425 days |
| **730 days** | ±60 days | 670—790 days |
| **3 years** | ±90 days | 1005—1185 days |
| **4 years** | ±90 days | 1370—1550 days |
| **5 years** | ±90 days | 1735—1915 days |
| **6 years** | ±90 days | 2100—2280 days |
| **7 years** | ±90 days | 2465—2645 days |
| **8 years** | ±90 days | 2830—3010 days |
| **9 years** | ±90 days | 3195—3375 days |
| **10 years** | ±90 days | 3560—3740 days |

## Table 6: Schedule of Events

| | Screening | Admission | Surgery | Discharge | 42 days [1] ± 7 days | 180 days [1] ± 30 days | 365 days ±60 days | 730 days ±60 days | 3 ,4, 5 years ±90 days[2] | 6, 7, 8, 9, 10 years [2] ±90 days | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Obtain Informed Consent** | X | | | | | | | | | | |
| **Review Inclusion/Exclusion** | X | | | | | | | | | | |
| **Demographics** | X | | | | | | | | | | |
| **Medical History** | | X | | | | | | | | | |
| **Randomization** | | | X[3] | | | | | | | | |
| **Device Log** | | | X | | | | | | | | |
| **Operative Data** | | | X | | | | | | | | |
| **Discharge Information** | | | | X | | | | | | | |
| **Harris Hip Score[9]** | X | | | | | X | X | X | X | | |
| **Concomitant Medications[9]** | | X | | X | X | X | X | X | | | X |
| **Radiology Imaging[10]** | | X | | X | X | X | X | X | X | | X[6] |
| **Metal Ion Testing[10]** | | X | | | X[6] | X[6] | X[6] | X[6] | X[6] | | X[6] |
| **EQ-5D-3L[8, 9]** | | X | | | | X | X | X | X | | |
| **HOOSv2 (includes WOMAC)[7,9]** | | X | | | | X | X | X | X | | |
| **UCLA Activity Score[8,9]** | | X | | | | | X | X | | | |
| **AEs & SAEs(including intra-operative) [9]** | | | X | X | X | X | X | X | X | X | X |
| **Hip Noise Assessments[7, 9]** | | | | | X | X | X | X | | | |
| **Forgotten Joint Score (FJS-12)[7, 9]** | | | | | | X | X | X | X | | |
| **Cross-Sectional Imaging[10]** | | | | | | X[6] | X[6] | X[6] | X[6] | | X[6] |
| **Subject Satisfaction[7, 9]** | | | | | | | X | X | X | X | |
| **End of Study[4]** | | | | | | | | | | X[5] | |
| **Post-operative Procedure Log[4]** | | | | | | | | | | | |
| **Device Deficiency[4, 9]** | | | | | | | | | | | |
| **Revision[4, 9]** | | | | | | | | | | | |

[1] Safety analyses will be performed when the last of the first 30 investigational Subjects passes 42 days and 180-day follow-up time points. A report will be submitted to the FDA 6 weeks after this cohort passes the respective follow-up time point.

[2] Evaluations at 6, 7, 8, 9, and 10 years will be performed by telephone or mail contact.

[3] Randomization should be performed as close to the time of surgery as logistically possible.

[4] May be performed at any time point as applicable.

[5] An End of Study form will be completed for all Subjects at the 10-year visit if not completed prior.

[6] If subject has a symptomatic study hip as defined in Section 7.3.

[7] For subjects with 2 enrolled hips, collect once *per hip.*

[8] For subjects with 2 enrolled hips, collect once *per visit.*

[9] Answers will be collected from subjects via electronic communication (phone, web conference, telemedicine) due to subject visit restrictions on in-office visits (see Section 8.12.8.5).

[10] For any abnormal findings (Metal ion levels and/or Imaging), subjects may be seen more frequently for monitoring of safety

#### *8.12.8.1 Screening*

The first visit is the screening visit.

Procedures to be completed at the Screening Visit:

- Obtain informed consent, place IC document in the Subject file, and give signed copy to the Subject;
- Assign a Subject Investigational Number and Subject code (Subject's initials or unique 3 letter code designated by the site);
- Collect data per CRF Completion guidelines;

If the Subject does not meet all inclusion/exclusion criteria, the Subject should not be enrolled in the study by the Investigator and the Subject will be considered a screen failure. The End of Study CRF will be completed to indicate the Subject was a screen failure. The reason for the screen failure will be recorded on the Screening and Enrollment Log and CRF.

#### *8.12.8.2 Admission*

Admission assessments must be performed after screening activities and prior to surgery. Admission radiographs may be obtained prior to screening according to the methodology and timing that is standard of care at the investigational site as long as the radiographs are taken within 6 months prior to surgery and include AP Pelvis and lateral views.

- The following procedures are performed during the visit:
- Perform radiology imaging (if not available within 6 months prior to surgery)
- Obtain and process blood sample for metal ion analysis
- Collect data per CRF Completion guidelines

#### *8.12.8.3 Surgery*

The following procedures are performed during the visit:

- Randomize Subject. Randomization should occur as close to surgery as logistically possible, but may be performed any time after screening and prior to surgery.
- Update information in the Screening and Enrollment Log
- Complete Device Accountability Log
- Perform THA
- Collect data per CRF Completion guidelines
- Obtain and record any AEs or SAEs

#### *8.12.8.4 Discharge*

- The following procedures are performed during the visit:
- Perform radiology imaging
- Collect data per CRF Completion guidelines
- Obtain and record any AEs or SAEs

### *8.12.8.5 42 Day—5 Year*

Perform study procedures per Schedule of Events

- Perform radiology imaging
- At 42 and180-days and later visits, obtain and process blood sample for metal ion analysis for symptomatic subjects.
- At 180-days, 365-days, 730-days and 5-years after implant surgery, obtain and process blood samples for unilateral subjects enrolled in the sub-study and all bilateral subjects (see Appendix I).
- Perform cross-sectional imaging (only for symptomatic subjects at 180-day follow-up time point or later)
- If subjects are prevented from attending an in-office visit due to site restrictions on study visits or if a subject is not comfortable with attending a visit even after the site restrictions are lifted during the COVID-19 pandemic (or any other pandemic which may result in site closures), the study staff will conduct a visit by a phone call or telehealth visit during the visit window. During this visit, the study staff will assess the subject per the assessments outlined in the Schedule of Events for each follow-up visit. The staff will also provide the subject self-reporting questions for them to complete/answer. The subject self-reporting questions will be provided to the subjects based on the preferred method of each subject, for example; e-mail, mail, or fax or the questions will be read to the subjects with all the possible responses. If a subject is unable or not willing to conduct neither an in-person visit or a telehealth visit, a phone call will be completed to collect safety, revision, and medication updates. The reason why a visit was not conducted do to COVID-19 will be recorded in the database.
  The following assessments will be completed using version 3.0 of the case report forms (CRFs) during either an in-person or Telehealth visit per the assessments specified for each follow-up visit timepoint, as outlined in the Schedule of Events (Table 6). Subject will be allowed to have radiographic or lab procedures performed at remote facilities, if deemed necessary due to the COVID pandemic, that are IRB approved locations and the facilities have been trained to the study procedures and data collection requirements.

  Study staff, including interviewers will be trained to the study protocol and to the data that needs to be collected at each of the follow-up visit. Interviewers will be instructed to read the question as they are on the CRFs and not provide subjects with additional interpretation. The telehealth visits will be conducted as standard of practice for each study site on conducting telehealth or phone call visits, using the same case report forms as it is for in-person visits.

  The following telehealth assessments will be modified as described below:

  Harris Hip Score – Subjects will provide their self-reported answers to questions (excluding the Trendelenburg, range of motion and leg length difference) unless otherwise evaluated by the investigator.

  Radiology Imaging - Subjects will be informed of the importance of this data and will be asked to have images taken at local radiology facilities.

Metal Ion Testing – Subjects will be informed of the importance of this data and will be asked to have labs taken at local lab facilities.

Hip Noise Assessments- Verbally reported by the subject and if possible auditory reproducible by the investigator.

In the event that radiology imaging and metal ion testing cannot be completed by the subject as requested, at a minimum safety, revision and medication updates will be reviewed during the phone call or telehealth visit.

NOTE: a subject will be asked to return to the office for a missed in-person or telehealth visit as soon as restrictions are lifted, even if the visit is out of the visit window. At the in-office visit, all procedures, including the Harris Hip Score and HOOS, will be completed.

- Collect data per CRF Completion guidelines
- Obtain and record any AEs or SAEs
- Revision status will be documented

Upon approval of Protocol (v8.0) by the FDA and IRB:

- All subjects randomized to the Control cohort will be notified that their participation in this clinical study has been concluded and no further study related exams will be performed, or data collected.

#### *8.12.8.6 6 Year – 10 Year*

Perform study procedures per Schedule of Events

- Collect data through telephone or mail contact per CRF Completion guidelines
- Follow Lost to Follow-Up procedures if unable to contact Subject and complete a Missed Visit form if necessary

#### *8.12.8.7 Unscheduled Visit*

An unscheduled visit may occur if the Subject presents with a symptomatic study hip outside of a study visit or follow up window or if a Subject is seen by one of the site staff in between study visits. The following procedures are performed during the visit:

- Obtain and record information about concomitant medications
- Obtain and record any AEs or SAEs
- Complete CRFs per CRF completion guidelines
- Obtain and process blood sample for metal ion analysis (for symptomatic subjects)
- Perform radiology imaging (for symptomatic subjects)
- Perform cross-sectional imaging (for symptomatic subjects at 180-day follow-up time point or later)

### 8.12.9 Investigational Device Accountability

The investigational site will maintain an inventory of the Investigational Device. The Device Accountability Log will include:

- Name of person designated as responsible for the inventory of the investigational product
- Amount received, including date and lot number
- Amount currently in inventory
- Devices dispensed to each Subject, identified by Subject code and subject identification number
- Non-study disposition (e.g. wasted, broken, destroyed) – destruction should not occur without prior notification and approval by the Sponsor
- Amount returned to Sponsor or designee, if applicable.

The Sponsor or its designee will provide forms to facilitate investigational product inventory control. These records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time.

Investigational Device shipment to sites will be accompanied by a Device Shipment Form which must be signed and dated upon receipt, and a copy sent back to the Sponsor. This form must be filed in the site regulatory binder. After the last Subject has enrolled at the site, the site will return the devices according to instructions from the Sponsor or its designee.

### 8.12.10 Post-Surgical Rehabilitation

Post-treatment rehabilitation procedures will be per standard of care at the investigational site.

## 8.13 Device Removal

Sponsor should be notified immediately when a revision of the Investigational or Control device is planned for any subject that has not previously been discontinued from the study. Sponsor or its designee will provide an explant retrieval kit and the site will return any revised components for retrieval analysis according to instructions. Any explanted Investigational devices must be logged on the device accountability log when explanted and shipped to the Sponsor or its designee. Blood will be collected for metal ion analysis, and radiographs and cross-sectional imaging will be taken prior to the revision procedure. In addition, tissue samples, if available, will be obtained for histological analysis.

### 8.13.1 Unilateral Subjects Who Undergo Device Removal

Subjects with only one hip replacement device (ODH or Control) who have undergone revision surgery will be withdrawn from the study and no additional follow-up visits will occur.

### 8.13.2 Bilateral Subjects Who Undergo Device Removal

When 1 hip is revised in subjects with the same bilateral hip devices (either ODH/ODH or Control/Control), the remaining hip will continue to be followed per the Schedule of Events above. In the event that the other enrolled hip also undergoes revision surgery, the subject will be withdrawn from the study and no additional follow-up visits will occur.

Subjects with different implanted hips (ODH/Other or Control/Other) will remain in the study as long as ODH or Control is implanted, pending termination of the Control arm upon approval of Protocol v8.0. In the event that the ODH or Control hip is revised, then the subject will be withdrawn from the study and no additional follow-up will occur.

## 8.14 Subjects Completion and Disposition

### 8.14.1 Screen Failure

Screen failure is defined as a Subject who has signed the IC document but does not have the assigned device implanted. Reasons for Screen Failure may include, but are not limited to:

- not meeting the eligibility criteria at any point before surgery
- Subject withdrawing consent for any reason at any point before enrollment
- Investigator decision (*ie*, not implanting the assigned device during surgery).

End of Study CRFs will be completed for all screen failures.

### 8.14.2 Withdrawn (Discontinued) Subject

Reasonable efforts to keep each Subject in the study will be made and must be documented by the Investigator. A Subject will be withdrawn from the study for any of the following reasons:

- Subject voluntarily withdraws consent after enrollment or terminates participation.
- The Investigator withdraws the Subject. If this decision is made for safety reasons or non-compliance with the study Protocol or procedures, the Sponsor will be notified immediately.
- The Investigator or the Sponsor stops the study or stops the Subject's participation for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and Good Clinical Practice.

For each case, detailed information will be obtained explaining circumstances leading to the withdrawal. This will be recorded on the End of Study Form.

### 8.14.3 Lost to Follow-up

A Subject will be considered lost to follow-up if he/she does not appear for two consecutive scheduled study visits or are unresponsive to the questionnaires and study personnel are unable to contact the Subject. 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 site's policies, but no less than 3 documented phone contacts and 1 certified letter without response. The first contact attempt must occur within 30

days of scheduled visit or follow up. These attempts to contact the Subject should be recorded in source documents and the End of Study Form completed. If a Subject returns for study visits or follow ups after being designated as lost to follow-up on the End of Study Form, study visits or follow ups should resume and Missed Visit CRFs should be completed for visits or follow ups that were not performed. The End of Study form will be revised as needed.

### 8.14.4 Completed Subject

A Subject will be considered as having completed the study when he/she has completed the 10-year visit. The End of Study Form will be completed for each Subject who completes the study.

## 8.15 Investigational Site Discontinuation

Study site participation may be discontinued if the Sponsor, the Investigator or the IRB/REB/EC/HREC of the study site determines it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and GCP.

## 8.16 Study Discontinuation

The study will be discontinued if the Sponsor decides it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and GCP. The Sponsor may also discontinue the study for no reason.

If the study has been discontinued for safety reasons, the Sponsor will advise the Investigators about the proper procedure to assure that the safety of the enrolled Subjects is maintained.

The IRB/REB/EC/HREC and regulatory agencies must be informed of the study status.

# 9 Statistical Procedures

## 9.1 Statistical Design and Hypotheses

This is a randomized controlled study of Investigational Device compared to the Control Device. The primary endpoint analysis is of the type of non-inferiority statistical design. No interim analyses of the primary endpoint are planned.

### 9.1.1 Statistical hypothesis for the primary endpoint

The primary hypothesis is that the proportion of unilateral Subjects classified as Overall Success in the Investigational Group treated with the Investigational Device (OXINIUM$^{\lozenge}$ DH Hip System) will be non-inferior compared to the proportion of unilateral Subjects classified as Overall Success in the Control Group treated with the commercially available hip replacement device at the 730-day time point after primary surgery for THA.

The study's null and alternative hypotheses are:

$$H_0: \pi_I - \pi_C \leq \delta;$$

$$H_a: \pi_I - \pi_C > \delta.$$

Where,

$\pi_I$ is a population proportion classified as overall success at the 730 day time point among the Subjects treated with the Investigational device; $\pi_C$ is a population proportion of unilateral Subjects classified as overall success at the 730 day time point among the unilateral Subjects treated with the Control Group Devices and, $\delta$ is the non-inferiority margin. The Type I error is set to one-sided .025.

The non-inferiority margin $\delta$ is set to -.1 (-10%), per the non-inferiority margin used in similar pivotal studies. Statistical definition of success is rejection of the $H_0$. The null hypothesis will be tested by constructing a two-sided 95% confidence interval for the difference in proportions of Subjects classified as overall success between the Investigational and the Control Group (Blackwelder WC. 1982). If the lower boundary of such interval does not include $\delta$, the null hypothesis will be rejected.

In cases where subjects are prevented from attending an in-office visit due to site restrictions on study visits during the COVID-19 pandemic (or any other pandemic which results in a site closure) and a telephone call is conducted instead, the data from the subsequent out of window in-office visit will be used for purposes of the primary analysis.

### 9.1.2 Study Success

Study success is defined as follows:

The Investigational device is non-inferior to the Control Device at the 730-day follow-up time point. Study Success will be met if the null hypothesis for the primary endpoint is rejected by the statistical testing described in Section 9.1.1.

### 9.1.3 Statistical hypothesis for the secondary endpoint

The secondary endpoint is the difference in Western Ontario and McMaster Universities Osteoarthritis Index v 3.0 (Likert) Functional Limitations Score between Admission (baseline) and the 730-day follow-up time points.

$\Delta WOMACFS_{b\text{-}730} = WOMACFS_{baseline} - WOMACFS_{730\ days}$

The statistical hypothesis is of non-inferiority type investigating non-inferiority of the Investigational Device over the Control Device. The appropriate statistical approach is to test a single one-sided null-hypothesis that the difference between the Investigational and the Control Arm is equal to or less than 0. Rejection of the null-hypothesis is consistent with non-inferiority of the Investigational treatment to the Control Device.

$H_0: \mu_I - \mu_c \leq \delta$

$H_a: \mu_I - \mu_c > \delta$

Where:

$\mu_I$ and $\mu_C$ are the means of the two independent normal distributions; $\mu_I$ is the mean population value of the $\Delta WOMACFS_{b\text{-}730}$ in the Subjects treated with the Investigational Device; $\mu_c$ is the mean population value of the $\Delta WOMACFS_{b\text{-}730}$ in the Subjects treated with the Control Device and $\delta$ of (-7.9) on a scale from 0 (best) to 100 (worst). The $\delta$ value of -7.9 is the literature established Minimal Clinically Important Difference for the WOMAC Functional Score (Tubach F et al., 2005). The hypothesis will be tested by a one-sided t-test at the alpha level of 0.025. If the hypothesis is rejected (i.e. non-inferiority is confirmed) superiority will be evaluated. The superiority will be evaluated by constructing the two-sided 95% confidence interval for the difference in mean values for $\Delta WOMACFS_{b\text{-}730}$ between the Investigational and the Control Groups.

The testing of the secondary hypothesis is not a condition for Study Success. The testing will be performed only if the $H_0$ for the primary endpoint has been rejected. The multiplicity adjustment approach for the secondary endpoint will be described in the Statistical Analysis Plan. If the testing of the secondary endpoint reaches rejection of the $H_0$, the Sponsor intends to make appropriate efficacy claims. The secondary analysis described above will be conducted separately for unilateral and bilateral subjects.

In cases where subjects are prevented from attending an in-office visit due to site restrictions on study visits during the COVID-19 pandemic (or any other pandemic which results in a site closure) and a telephone call is conducted instead, the data from the subsequent out of window in-office visit will be used for purposes of the primary analysis..

### 9.1.4 Statistical approaches for other endpoints

Other outcomes will be evaluated through the 3-year follow-up time point, separately for unilateral and bilateral subjects, using a series of exploratory analyses based on superiority approaches. For quantitative outcomes this will be based on two-way repeated measurement Analysis of Covariance or two-way repeated measurement Analysis of Variance for outcomes without baseline value. For categorical outcomes the analyses will be based on Fisher Exact and Chi-Square tests. Differences in revision rates in the Investigational and the Control Groups will be evaluated using Log-rank test and Kaplan-Meier survival estimates and, Incidence Rate Ratios based on Poisson distribution. Descriptive summary statistics by treatment Group will be provided for all endpoints. For quantitative variables this will include mean, standard deviation, median, minimum and maximum values. For categorical variables this will include counts and percentages. Furthermore, aggregated categories will be created for quantitative variables for which such algorithm exists in the literature (e.g. “poor”, “good”).

### 9.1.5 Additional Analysis

Due to the COVID-19 pandemic (or any other pandemic which results in a site closure), it is expected that Protocol Deviations will occur that may cause out of window in-office follow-up visits. Note that because the missed visit telephone survey will ensure that the key information needed for the primary analysis at the 2-year follow-up visit (i.e. device survivorship) is

collected, the impact of this missing data on this component of the primary analysis is expected to be minimal. However, some Harris Hip Scores (HHS) and radiographic endpoints are likely to be missing or out of window. In order to evaluate the impact of out of window visits incurred by the COVID-19 pandemic on the primary, secondary and other endpoint analyses at the 2-year follow up time point, the following additional analysis will be performed:

1. A within subject comparison of the total HHS score (excluding Range of Motion assessments) data from in person visit compared to the telephone visit at the 2-year follow-up visit, for each treatment group separately by use of a paired t-test or Wilcoxon signed rank test depending on normality assumptions.
2. A within subject comparison of the total HOOS score data from in person visit compared to the telephone visit at the 2-year follow-up visit, for each treatment group separately by use of a paired t-test or Wilcoxon signed rank test depending on normality assumptions.
3. Comparison of data (including radiographic endpoints, UCLA, EQ-5D-3L, FJS-12) at the 2-year follow-up visit for subjects within and out of window at the 2-year visit due to COVID-19 pandemic for each treatment group will be conducted. For endpoints with continuous data, two sample t-test, Wilcoxon rank test or two factor generalized linear model will be used. For endpoints with categorical data, Fisher's Exact test or Chi-Square test will be used.

It is expected that the HHS, radiographic, and survivorship profiles of the subjects with and without out of window data at the 2-year visit will be similar, and that any missing data due to data restrictions associated with COVID-19 will not bias study conclusions.

Should follow up visits at further time points be impacted by the COVID-19 pandemic, the above analysis will be repeated at those time points.

## 9.2 Statistical approaches for analysis of adverse events

Adverse events will be by time to occurrence and relationship to device and surgery, separately for unilateral and bilateral subjects. Adverse events will be divided into intra-operative, post-operative systemic and post-operative site events. Rates of adverse events will be compared between the Groups through the 3-year follow-up time point using the Fisher exact test. A comparison of adverse events at all time points for subjects within and out of window at the individual visit for reasons due to the COVID-19 pandemic (or any other pandemic which results in a site closure) will be performed. Proportions of subjects with one or more AE, SAE, Device-Related AE, and Procedure-Related AE (each type separately) will be compared at each time point using a Fisher's Exact Chi-Square test.

## 9.3 Analysis of staged enrollment data

Staged sample includes 30 Investigational Subjects and, approximately, 30 Control Subjects. The actual number of Control Subjects may differ due to randomization sequence balancing properties. The safety information will be tabulated by type of event and study group. The rates of safety events between the Groups will be compared using the Fisher exact test.

## 9.4 Randomization Plan

Randomization will be performed at a 1:1 ratio between the Investigational and Control Groups. Randomization will be carried out according to the blocks procedure. Block randomization is used to assign eligible Subjects to the treatment Groups in order to avoid imbalance in the number of Subjects assigned to each Group within a site. The pattern of the blocks will be concealed to avoid selection bias. Two block sizes will be used, with 2 and 4 Subjects per block. Block sizes will be chosen at random. This scheme makes breaking the blinding by working out the block pattern extremely difficult and reasonably protects against biased allocation of Subjects.

For subjects that require the contralateral hip to be replaced during study participation, no second randomization is required; the contralateral hip is assigned the same hip system as the first hip enrolled for the subject

No site will be allowed to enroll more than 20% of the overall sample.

## 9.5 Sample size estimate and statistical power

The sample size is calculated using the following formula:

$$n = f(\alpha, \beta) \times [\pi_c \times (1 - \pi_c) + \pi_i \times (1 - \pi_i)] / (\pi_c - \pi_i - \delta)^2$$

where,

$\pi_c$ is the proportion of unilateral Subjects classified as overall success in the Control Group,

$\pi_i$ is the proportion of unilateral Subjects classified as overall success in the Investigational Group,

$\delta$ is a non-inferiority margin, and

$f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$ where

$\Phi^{-1}$ is the cumulative distribution function of a standardized normal deviate.

The sample size of 308 Subjects will have 80% power to reject the primary null hypothesis under the assumption of zero difference between the Investigational and Control Groups and proportion of overall success of .89. The estimate of the success rate is based on the data available on file with the Sponsor from similar clinical studies. The actual sample size will be increased for 15% to accommodate for unilateral Subject attrition.

In addition, the total sample size will be increased by a further 10% to allow for bilateral subjects while preserving the required power for analysis of unilateral-only subjects. Thus, this study will include 412 Subjects (206 in the Investigational and 206 in the Control Groups, respectively).

Following approval of Protocol v8.0, only the 205 subjects enrolled in the Investigational Group will continue to be followed.

## 9.6 Analysis Populations

For definitions of Subjects' status in the study see Section 8.14.4.

### 9.6.1 Intention-to-Treat

Consenting Subjects who qualify and are enrolled into the study (i.e. enrolled Subjects) will be included in the Intent-To-Treat (ITT) secondary analysis population, regardless of whether they receive the Investigational or Control Device and regardless of a subject's withdrawal from treatment or protocol deviation. Enrollment is defined as undergoing surgery and having the Investigational or Control Device implanted. Values for the enrolled Subjects who do not have the 730 day end point will be imputed to create a complete ITT population.

### 9.6.2 Modified Intention-to-Treat

The modified Intent-To-Treat (mITT) population is defined as all enrolled Subjects who receive the investigational device and have any follow-up. The mITT population will be used for safety analyses.

### 9.6.3 Per-protocol Population

The Per-protocol population (PP) population includes all enrolled subjects who received the Study (Protocol) treatment and do not have major protocol deviations. Examples of major protocol deviations include Subjects not signing the Informed Consent document, missing radiographic evaluation at Discharge, missing HHS at Screening, and not implanting the assigned device (specifically, Control implanted instead of Investigational or Investigational implanted instead of Control). Any visits where protocol deviations occurred will be reviewed for possible exclusion from the PP population. The per-protocol population will be used for primary analysis.

The Subjects with major protocol deviations that are excluded from the PP population will be tabulated by violation type and affected visit(s), where applicable.

### 9.6.4 Primary Analysis Populations

Primary analysis will be performed on the PP population. Secondary analysis will be performed on ITT population. Detailed safety analysis will be performed on the mITT population.

### 9.6.5 Unilateral and Bilateral Subjects

Unilateral subjects are defined as enrolled subjects who do not undergo a THA on the contralateral hip.

Bilateral subjects are defined as enrolled subjects that undergo a THA on the contralateral hip.

NOTE: When defining unilateral and bilateral subjects above, THA does not include revision surgery.

Analysis of the primary endpoint will be conducted using the analysis populations as described in 6.6.4 for unilateral subjects only.

Analysis of the secondary and other endpoints will be conducted using the analysis populations described in 6.6.4, with each analysis also separated into unilateral and bilateral subjects. The two populations of bilateral subjects are: 1) subjects with the same hip system in each hip

(ODH/ODH and Control/Control) and 2) subjects with different hip systems in each hip (ODH/Other and Control/Other).

### 9.6.6 Handling of Missing Values

Values for the enrolled Subjects who do not have the 730-day time point will be imputed to create a complete ITT population for the analysis, where applicable.

In cases where subjects are prevented from attending an in-office visit due to site restrictions on study visits during the COVID-19 pandemic (or any other pandemic which results in a site closure) and a telephone call is conducted instead, the data from the subsequent out of window in-office visit will be used. In cases where the subject does not return to the office for the missed visit as soon as restrictions are lifted, but has provided data through a within-window telephone call, then the data collected during the telephone call will be used for purposes of analysis at that follow up visit.

The missing values imputation approach is shown in **Error! Reference source not found.** below.

**Table 7: Missing values imputation approach by endpoint**

| Endpoint | Imputation Approach |
|---|---|
| Overall Success (Composite) | No imputation |
| HHS total score at 730 day time point | Multiple Imputation Technique |
| Radiologic success at 730 day time point | LVCF approach of 365 days follow-up or later observation is available |
| Absence of revision at 730 day time point | LVCF approach of 365 days follow-up or later observation is available |
| Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) | Multiple Imputation Technique |
| EQ-5D | Multiple Imputation Technique |
| Hip Disability and Osteoarthritis Outcome Scores v2.0 (HOOS) | Multiple Imputation Technique |
| Forgotten Joint Score (FJS-12) | Multiple Imputation Technique |
| UCLA Activity Score | Multiple Imputation Technique |
| Subject Satisfaction with Outcome | LVCF approach of 365 days follow-up or later observation is available |
| Hip Noise Evaluation Questionnaire | LVCF approach of 365 days follow-up or later observation is available |
| Radiology outcomes | LVCF approach of 365 days follow-up or later observation is available |
| Metal ion concentration in whole blood | Multiple Imputation Technique |

The imputation will target the entire missing sub scale or overall score value and not the individual questions (items) composing the score.

The statistical parameters for the imputed samples will be estimated by SAS PROC MIANALYZE. (Barnard, J, 1999)

Prior to imputation, missing cases will be classified into Missing at Random (MAR)/ Missing Completely at Random (MCAR) and not-Missing-at-Random (nMAR). Differentiation between the MAR and MCAR does not have implication for multiple imputation procedure. nMAR cases have a specific reason for missing data such as Protocol Deviations, emerging comorbidities, AEs, deterioration of health and functional status will be reviewed qualitatively in order to assist in

classifying Subjects into the nMAR category. Only the MAR/MCAR will be imputed using the SAS PROC MI. nMAR cases will be treated as

(i) excluded from the analysis and

(ii) imputed using the specific value for each case based on the circumstances for missing values.

All imputed samples will be analyzed under the ITT population. Sensitivity analyses will be performed to verify assumptions used in selection of nMAR observations. Specifically, an analysis will be performed in which nMAR Subjects are treated as MAR/MCAR observations. Additional sensitivity analyses will include tipping point analysis for the Overall Success. A distribution list of missing data and follow-up visits completed will be summarized by treatment group in order to evaluate the comparability of missing data over time between the Investigational and Control Groups.

## 9.7 Poolability of the data

Data pooling across the geographical location and sites will be justified on a basis that the sites will follow the same protocol, will be monitored in the same fashion, and will have data gathered and validated with the same mechanisms.

### 9.7.1 Poolability across geographies

This study will be conducted in the United States (US) and countries out of the United States (OUS). The primary statistical analysis will use the data from all geographical locations as one cohort. The similarity of US and OUS Subjects with respect to important demographic or other variables, either known or suspected to have an influence on the outcome variables will be evaluated. The absence of similarity will, however, not prevent pooling of the data. Comparability analyses will be performed with a two-sided test with a significance level of 0.05.

The poolability of the data between US and OUS sites will be investigated for the variable Overall Success using the multiple logistic regression and the independent factors LOCATION (US and OUS), GROUP (Investigational and Control), and LOCATION*GROUP interaction. Significant LOCATION*GROUP interaction would indicate a need to use the variable LOCATION as a covariate in the main analysis.

Poolability across Investigational sites

To verify that the treatment effect is consistent across the sites, analyses for the primary efficacy endpoint will be performed to investigate the differences between the sites and presence of SITE*GROUP interactions. Smaller study sites with insufficient numbers of Subjects to allow a meaningful analysis will be combined into one or more pseudo-sites to allow the comparison to be done. The size of any pseudo-site created in this way will not exceed the size of the study site with the largest enrollment. This analysis is based on logistic regression. Presence of significant SITE*GROUP interaction will be used as an indicator for further investigation and possible

indication for sensitivity analysis. Overall Success by SITE and GROUP will also be tabulated for exploratory purposes.

# 10 Adverse Events and Device Deficiency Reporting

## 10.1 Definitions

### 10.1.1 Adverse Events

Adverse event (AE) is defined as any untoward medical occurrence associated with the use of an investigational product in humans and that does not necessarily have a causal relation with the investigational product. AEs can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

### 10.1.2 Serious Adverse Events

An adverse event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Led to death,
- Led to serious deterioration in health of the Subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function including chronic disease, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or congenital abnormality or birth defect including physical or mental impairment
- Required Intervention to Prevent Permanent Impairment or Damage, or
- Other serious events that do not fit the other outcomes, but the event may jeopardize the Subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

For Adverse device event (ADE) and Device deficiency (DD), date of occurrence, and details of the product/procedure related to the event will be included and where applicable, pictures taken of the device. The deficient product should be retained for return to S+N. Updates to submitted information will be recorded in the CRF.

All adverse events will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

The investigator will inform the regulatory agency and IRB/IEC of adverse events as per the requirements listed below:

Within 24 hours of becoming aware of an SAE, the Investigator must complete the SAE report (providing as much information as is immediately available) and submit to the Sponsor. Follow-up reports must be submitted to the Sponsor as additional information becomes available. The Investigator must also report all SAE's to the IRB/REB/EC/HREC, as required by the IRB/REB/EC/HREC.

Unanticipated SADE's and DD's that could have led to SADE will be reported to IEC/IRB and regulatory authorities within 10 working days after the investigator first learns of the effect.

All other events will be reported on a periodic/annual basis.

Depending on the nature of the adverse event, S+N may request copies of the subject's medical records, imaging, operative notes, as well as results of any relevant laboratory tests performed, or other documentation related to the AE. If the subject was hospitalized, a copy of the discharge summary may be requested by S+N and should be forwarded as soon as it becomes available. In certain cases, S+N also may request a letter from the Investigator that summarizes the events related to the case. Refer to the ISF Sponsor Contact Information Sheet to report SAE, unanticipated SADE, anticipated SADE, and DD.

### 10.1.3 Serious Adverse Device Effects

A serious adverse device effect (SADE) is any adverse device effect that has resulted in any of the consequences characteristic of an adverse event.

The Investigator must report SADEs according to SAE reporting requirements.

### 10.1.4 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is 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, investigational brochure or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects (21 CFR 812.3(s)). UADEs must be reported by the clinical Investigator to the Sponsor and the reviewing IRB/REB/EC/HREC, as described below:

Investigators are required to submit a report of a UADE to the Sponsor and the reviewing IRB/REB/EC/HREC as soon as possible, but in no event later than 10 working days after the

Investigator first learns of the event (21 CFR 812.150(a)(1)). Follow-up reports must be submitted to the Sponsor as additional information becomes available.

Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to the FDA, all reviewing IRB/REB/EC/HREC, and participating Investigators within 10 working days after the Sponsor first receives notice of the effect (21 CFR 812.46(b), 812.150(b)(1)).

### 10.1.5 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling (ISO 14155). Device deficiencies may occur before surgical use, during surgical use, or after surgical use. All Smith & Nephew device deficiencies (including instrument deficiencies) will be collected throughout the study and captured on the Device Deficiency CRF.

The Investigator will assess the device deficiency and report whether it was related to an AE or if it could have led to an AE if intervention had not been made. If an Investigator indicates that the device deficiency was related to an AE or if the Sponsor determines the device deficiency was related to an AE, the internal cross-functional team will review the AE and deficiency. Any intraoperative delay that was caused by the device deficiency will be collected as well as if the device or instrumentation will be returned for evaluation.

The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity (if applicable). DDs will undergo independent safety review by the Adverse Event Monitoring board and be evaluated for relationship to reported AEs and potential to cause SADE. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee:

- ADE and DD – without unreasonable delay
- SAE, SADE, and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event)

All other events – according to usual timescale

## 10.2 Documentation of Adverse Events

Adverse Events (AEs) will be collected throughout the study and all AEs will be captured. The Investigator or designee will record all AEs on the appropriate CRFs. Investigators are responsible for reporting all Device Deficiencies, AEs, ADE, SAEs, SADEs, and UADEs. Adverse events will be categorized according to the definitions in Table 8 below.

**Table 8: Adverse Event Categorization**

| | NOT DEVICE-RELATED | DEVICE- OR PROCEDURE- RELATED | |
|---|---|---|---|
| **Non-Serious** | **Adverse Event (AE)** | **Adverse Device Effect (ADE)** | |
| **Serious** | **Serious Adverse Event (SAE)** | **Serious Adverse Device Effect (SADE) (See 10.1.3)** | |
| | | **Anticipated** | **Unanticipated** |
| | | **Anticipated Serious Adverse Device Effect (ASADE)** | **Unanticipated Serious Adverse Device Effect (USADE)** |

The Investigator will assess Subjects at each study visit for the occurrence of AEs. In order to avoid bias in eliciting AEs, Subjects should be asked non-leading questions. All AEs, regardless of severity, reported by the Subject or found on examination or laboratory report, must be recorded.

All AEs must be followed until resolution is reached. All treatments and outcomes of the AE must be recorded.

All AEs and SAEs in the investigational arm must be followed until:

- AE is resolved (i.e. return to normal/baseline values)
- Subject is lost to follow-up or withdraws consent
- Subject completes study, including required follow-up visits
- Study closure

The unresolved AEs and SAEs pertaining to the control arm will not be followed under protocol version 8.0. The Investigator must, following GCP guidelines, continue to treat (or refer Subject to an appropriate practitioner for continuing treatment of) any AE that remains unresolved after the Subject has completed study participation.

The severity of all AEs will be categorized 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 well-being.

- **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 well-being 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 must assess causality of AE in relation to study procedure or using of the study product as: unrelated, possible, and definite based on the following definition:

- **Unrelated**: The AE is definitely not associated with the study procedure or use of the study device
- **Possible**: There is evidence to suggest the casual relationship between the study procedure or use of the study device and the AE.
- **Definite**: The AE was caused by the study procedure or use of the study device.

## 10.3 Evaluation of Adverse Events

The Sponsor will form an internal cross-functional team to review adverse event listings, metal ion results and noise assessment results. The internal cross-functional team will include a medical safety representative. The first Subject from each site will be reviewed. Based on the volume of enrollment, the internal cross-functional team will meet, at a minimum monthly, during active enrollment and quarterly thereafter. Adverse events will be internally reviewed by the internal cross-functional team through the automated adverse event routing system and will be stored in the internal global safety tracking database which tracks the internal classification, escalation, and results of the safety review board. Any unexpected events or trends will be further reviewed by independent consultants.

An ad hoc safety review group of consultants will be formed to independently assess any unexpected findings identified by the internal cross-functional team. Recommendations by this safety review group will be reviewed by the Adverse Event Monitoring Board and followed up immediately with appropriate actions up to and including pausing or stopping the study.

## 10.4 Reporting of Adverse Events

If applicable, the Sponsor will submit progress reports to Investigators to provide to their reviewing IRB/REB/EC/HRECs and (if applicable) to the FDA at least annually and more frequently if required.

Sponsor will inform all Investigators in writing about SAEs, SADEs, and UADEs occurring in clinical investigations that have been reported to the Sponsor according to regulatory requirements. The Sponsor will complete all additional reports required by 21CFR 812.

# 11 Reporting and Publication of Results

All unpublished information given to the Investigator by Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

No patent application(s) based on the results of the study may be made by the Investigator nor may assistance be given to any third party to make such an application without the written authorization of Sponsor.

The publication of results in the academic journals will be guided by the Site Agreements between the Sponsor and the Investigator.

The study is registered on clinicaltrials.gov.

# 12 Investigator Responsibilities

Investigator responsibilities are defined in Title 21 of the US Code of Federal Regulations Part 812, Subpart E, in relevant regulatory guidelines of other countries, in ISO 14155, and in GCP guidelines.

The Principal Investigator will comply with the commitments outlined in the in the Statement of Investigator, provided by the Sponsor/within the Clinical Trial Agreement, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in section 12 of this protocol. Sub-Investigators, who are individual member of the investigation site team designated and supervised by the Principal Investigator at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions, may have responsibilities delegated to them by the Principal Investigator. However, the Principal Investigator retains overall responsibility for the clinical investigation at the site.

In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

## 12.1 Investigator Qualifications

Investigators shall have proper medical qualifications, training, and licensure to perform the clinical duties involved in the study. Investigators shall have Human Subjects Research Protection or equivalent training. Finally, Investigators shall allocate sufficient time to perform duties involved in this clinical study, to delegate duties to qualified research staff, to supervise the research team and to maintain the facility qualified for the study.

## 12.2 IRB/REB/HREC/EC Ethical Approval

This study must have initial and continuing approval (when applicable) from an IRB/REB/EC/HREC responsible for approving clinical studies or from such body responsible for overseeing clinical investigations in the respective country where the investigation is conducted. This can be a local or a central IRB. Furthermore, no study activities, including -screening of Subjects may commence until the IRB/REB/EC/HREC approval letter is received by the Sponsor. A copy of the approval letter must be filed on-site in the site's regulatory binder. Where appropriate, amendments to the Protocol will be submitted for IRB/REB/EC/HREC review and approval before implementation.

## 12.3 Protocol Adherence

The Investigator agrees to conduct the study in accordance with this Protocol. Prior to initiating the study, the Investigator must sign and return the Investigator Agreement and the Protocol Signature Page of this Protocol.

An Investigator may not make any changes to the Protocol or study procedures, without first receiving written approval from the Sponsor and the IRB/REB/EC/HREC, except when necessary to eliminate apparent immediate hazards to a Subject. The Sponsor must receive FDA approval for significant changes to the Protocol or study procedures.

Protocol deviations will be reported as described in Section 15.3

## 12.4 Review of Source Documents

The Investigator agrees that the Sponsor's employees or designees, as well as representatives of FDA, Health Canada and regulatory agencies in the countries where the investigation is conducted will have the right to audit and review pertinent Subject files and medical records relating to this clinical study.

## 12.5 Record of Investigational Device Inventory

The Investigator will maintain a Device Accountability Log of all Investigational Devices received, used or returned during this study. The Device Accountability Log should be available during all monitoring visits. All Investigational Devices not used in this study must either be returned to the Sponsor at the completion of the study (or earlier at the Sponsor's request) or, with written permission, may be destroyed at the site. All explanted devices must be returned to the Sponsor according to the Sponsor provided protocol for handling of explanted devices.

## 12.6 Data Recording and Record Retention

- Data will be available in source documentation for each Subject enrolled in the study. Case report forms (CRFs) may be used as source documents if they represent data collected for the study and are where data were initially recorded. Subjects will record their responses directly on the following CRFs:
    - EQ-5D-3L
    - UCLA Activity Scale

  - HOOS
  - Hip Noise Assessment
  - Forgotten Joint Score
  - Subject Satisfaction
- The Sponsor will review completed source documentation, including CRFs. The Investigator will ensure that source documents, including Subject medical records, are made available for review by the Study Monitor and/or regulatory agencies, as required.
- Subject study records will not be destroyed without authorization from the Sponsor. This includes the following documentation:
  - CRFs, IC, and all study logs and forms
  - Investigational Device Accountability Logs and Investigational Device shipment receipts of all products shipped to the site
  - Correspondence with the ethical boards, Sponsor, FDA, Health Canada or other regulatory agency, Study Monitor or other Investigators
  - Study Protocol (all versions, if applicable)
  - Protocol and IC approvals from the ethical boards
  - Clinical Study Agreement and curricula vitae of Investigator(s) and other staff and the Study Delegation Log
  - Protocol Deviations
  - Source documentation that supports the data collected from each Subject
  - All study documents in ICH/GCP Section 8: Essential Documents for the Conduct of a Clinical Study
  - All study documentation as specified by the applicable regulatory requirement(s)

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 clinical 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. 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 investigational 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. In some circumstances the IRB/REB/EC/HREC will designate a custodian. 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.

# 13 Site Data Collection and Quality Control

## 13.1 Completing and Signing Paper Case Report Forms

All required data will be recorded on the CRFs provided by Sponsor. The CRF will be completed legibly in black or blue ink, with reasons given for missing data. All CRFs must be kept in good order and updated so they always reflect the latest observations on the Subjects participating in the study. Any corrections to the data will be made in a manner that does not obscure the original entry and will be dated and initialed by the Investigator or assigned designee. Data Submission CRFs will be signed and dated by the Investigator at the end of each study interval. In addition, the End of Study CRF will be signed and dated by the Investigator when a subject has completed or exited the study.

CRFs completed by the independent radiographic reviewer will be signed and dated by the reviewing radiologist.

## 13.2 Electronic Case Report Forms

All requirements for using an electronic system to capture, edit, store and retrieve study data will be met. This includes electronic systems that may be used by vendors, such as the independent radiologist, to collect, edit, transfer and store study data and associated digital signatures. Data will be entered into the electronic database in a timely manner by the study site and reviewed during routine monitoring visits as outline in the Monitoring Plan. The electronic database will be validated and verified and will maintain the protection of subject privacy. Electronic signatures will adhere to 21 CFR Part 11. The methods and procedures for cleaning the data through queries and source data verification, soft lock, quality control and database lock of the database before the start of the analysis is outlined in the Data Management Plan.

The archiving of the study records, including the study data will be maintained for a period of five years after the date the investigation is completed or terminated.

## 13.3 Transfer of CRF and Data Entry

The Investigator will submit completed CRFs to the Sponsor per Sponsor's instructions. All data will be entered into the study database.

The Sponsor or its designee will promptly review all submitted CRFs to identify inconsistent or missing data. Identified inconsistencies will be addressed via queries to the site.

# 14 Study Monitoring

Monitoring activities will be performed both on- and off-site according to GCP guidelines. The Study Monitor (or other Sponsor representative) will conduct the Site Initiation Visit, Interim Monitoring Visits, and a Close-Out Visit for each site. Sites may also have a Site Qualification Visit conducted by the Sponsor (or other Sponsor representative).

## 14.1 Site Qualification Visit

The Monitor or other Sponsor representative will ensure that the Investigator clearly understands and accepts the obligations incurred in undertaking this clinical study. Prior to the initiation of the clinical study, the Monitor or Sponsor may visit the clinical site to ensure that the Investigator:

- Understands the nature of the Protocol
- Understands the requirements for an adequate and well-controlled study
- Understands and accepts the obligation to conduct the clinical investigation in accordance with applicable sections of Title 21 of CFR, ISO 14155, and/or any other applicable regulation
- Understands and accepts the obligation to obtain IC in accordance with 21 CFR Part 56
- Understands and accepts the obligation to obtain IRB/REB/EC/HRER approval before the investigation may be initiated and to further ensure a continuing review of the study by the IRB/REB/EC/HREC in accordance with CFR 21 Part 56, and to keep the Sponsor informed of such IRB/REB/EC/HREC approval and subsequent IRB/REB/EC/HREC actions concerning the study
- Has access to an adequate number of suitable Subjects to conduct the investigation
- Has adequate facilities and staff for conducting the clinical investigation
- Has sufficient time from other obligations to carry out the responsibilities to which the Investigator is committed by applicable regulations

## 14.2 Site Initiation Visit

The monitor will visit each study site at least once before the beginning of the clinical study. No screening or other study procedures may be performed before the Initiation Visit.

## 14.3 Interim Monitoring Visits

The Sponsor will assure throughout the clinical study that the Investigator's obligations, as set forth in applicable regulations and in GCP guidelines, are being fulfilled and that the facilities used in the clinical study continue to be acceptable The Study Monitor will conduct site visits to ensure that:

- Facilities/staff used by the Investigator continue to be adequate for purposes of the study
- The study Protocol is being followed
- Protocol Amendments (if applicable) have been reported to and approved by the IRB/REB/EC/HREC
- Accurate, complete and current records are maintained
- Accurate, complete and timely reports are made to Sponsor and the IRB/REB/EC/HREC
- The Investigator is carrying out the agreed upon activities and has not delegated them to other unspecified staff

During periodic visits, the Monitor will compare a representative number of Subject records, CRFs and other supporting documents with the Investigator's reports to determine that:

- The information recorded is complete, accurate and legible
- There are no omissions of specific data elements

- Missing visits or examinations are noted and an acceptable rationale is reported
- Subjects failing to complete the study and the reason for each failure are noted
- IC has been documented in accordance with 21 CFR Parts 50 and 56, GCP or other applicable regulations

### 14.4 Close-Out Visit

The Monitor will conduct the close-out visit when:

- All participants enrolled at the site have completed study-related activities; or
- The site or entire study has been terminated for any reason; and
- A reasonable amount of time has been given to the site to complete data collection and to resolve outstanding discrepancies.

### 14.5 Direct Access to Source Documentation

The Study Monitor must be allowed direct access to source documentation for the purpose of verifying that the data in the CRFs are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with investigational staff. The Sponsor expects that the relevant investigational staff, including the Investigator and Study Coordinator(s), will be available, the source documents will be accessible and a suitable environment will be provided for review of study-related documents during monitoring visits. The monitor will meet with the Investigator to provide feedback on the conduct of the study.

## 15 Document Control

### 15.1 Responsibility

The Sponsor is responsible for document control of the initial Protocol and Protocol amendments. The Protocol and Protocol amendments will be initiated and signed off by the Sponsor.

### 15.2 Protocol Amendments

No changes to the IRB/REB/EC/HREC approved Protocol are allowed except when removing immediate threats for Subject safety. Any change to the Protocol made to protect the life and well-being of the enrolled subjects must be reported to the Sponsor according to regulatory requirements.

### 15.3 Protocol Deviations

A Protocol deviation is a non-adherence to the Protocol including deviations from Inclusion/Exclusion criteria, Subject not receiving the assigned study device (only applies if a subject randomized to one study group gets a device from the other study group during surgery), protocol defined measurement methodology as it pertains to radiographic interpretation or clinical outcomes, primary efficacy variables and/or GCP guidelines. Protocol deviations are to be reported to the Sponsor. Protocol deviations that affect Inclusion/Exclusion criteria, primary

efficacy variable or GCP guidelines will be reported to the Sponsor immediately. Protocol deviations will be recorded at the site and reported to the IRB/REB/EC/HREC as required.

The Investigator may implement a deviation from, or a change in, the Protocol to eliminate an immediate hazard(s) to study Subjects without prior IRB/REB/EC/HREC approval. As soon as possible, the implemented deviation or change, and the reasons for it, should be submitted:

- To the IRB/REB/EC/HREC for review and acknowledgement;
- To the Sponsor and, if required;
- To the regulatory authorities.

## 16 Protocol Amendments

Amendments should be made only in necessary cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the IRB/REB/EC/HREC. Protocol amendments need to be approved by the IRB/REB/EC/HREC and Regulatory Authorities, according to the applicable requirements prior to implementation at the site.

## 17 Confidentiality of the Study

The confidentiality of this study and associated documents is governed by the terms of the Clinical Trial Agreement.

## 18 Statements of Compliance

The investigation was conducted in compliance with applicable requirements in the protection of human subjects' regulations in 21 CFR part 50, GCP, the institutional review boards regulations in 21 CFR part 56 and the investigational device exemptions regulations in 21 CFR part 812.

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; ISO 14155: Clinical investigation of medical devices – Good Clinical Practice.

This clinical study will not commence until the required approval/favorable opinion from the IRB/REB/EC/HREC or regulatory authority has been obtained. Any additional requirements imposed by the IRB/REB/EC/HREC or regulatory authority will be followed.

Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies.

The clinical study is financed by the sponsor. All financial arrangements between the sponsor and investigation sites/investigators are documented separate clinical trial agreements.

# 19 Publication Policy

## 19.1 Publication of Study Data

The study is registered in clinictrials.gov, a publicly accessible database and the results will be made available within that database.

The results of this study may be submitted for publication within a manuscript.

The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.

## 19.2 Data Sharing

Smith+Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. Smith+Nephew, therefore, supports the data sharing requirements of The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017. In accordance, Smith+Nephew will consider requests to share individual (de-identified) participant data that underlie the results of any interventional clinical trial, as presented from the 1st July 2018 within an ICMJE associated journal. Requests made by researchers who provide a methodologically sound proposal will be considered. Requests may include data that underlie results presented in text, tables, figures, and appendices, together with data dictionaries. Availability of these data will begin nine months and end 36 months after article publication. Data supplied may only be used by the researcher(s) named in the approved research proposal for the purposes of achieving the aims of the analyses specified therein. All proposals should be directed to datasharing.gcs@smith-nephew.com. To gain access, data requestors will need to sign a data access agreement.

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# Appendix I – Metal Ion Sub-Study

## 1. Purpose of the Metal Ion Sub-Study

The purpose of the metal ion sub-study is to have the ability to detect if there are differences in metal ion concentration in whole blood between the Investigation and Control Groups. In addition, the sub-study will provide the ability to compare metal ion concentrations of symptomatic Subjects to non-symptomatic Subjects.

## 2. Site Selection

The sub-study will be conducted at 2 to 4 selected investigational sites in the U.S. based on site ability to quickly initiate the study and having facilities and personnel capable for participation in the sub-study.

## 3. Subject Enrollment

A limited number of unilateral subjects will participate in this sub-study while all bilateral subjects will participate in this sub-study. Enrollment has been completed for unilateral subjects.

### 3.1 Unilateral Subjects

A total of 70 consecutive Subjects (35 Investigational and 35 Control) from 2 to 4 sites in the U.S. will participate in the sub-study based on consecutive enrollment date across the participating sites. Subjects will be assigned to the sub-study until the sub-study is fully enrolled. Investigational sites will be notified of a Subject's assignment to the sub-study after the Subject has been enrolled and prior to the 180 day follow-up visit.

Based on data available to the Sponsor (data on file with the Sponsor), the expected standard deviation for the concentration of Zirconium under the rank procedure explained in Section 5 will be about 16 and the within group differences varied from 8.75 to 29.5. Under these assumptions, a sample size of 30 Subjects will have 80% power to detect difference in the averaged ranks of 10 if the within group correlation is .3 using a t-test of paired samples estimation method. The sample size of 30 Subjects in each Group will have 80% power to detect between Group differences in averaged ranks of 12 using a t-test for independent sample estimation method. The sample size estimation based on the t-test approach is a conservative estimate based on the data available to the Sponsor. Additional statistical analysis methods such as ANOVA and ANCOVA will be used in the analysis of the sub-study as described in Section 5 of Appendix I below.

The actual sample size of the metal ion sub-study will be increased for 15% to accommodate for Subject attrition and will include 70 Subjects (35 in the Investigational and 35 in the Control Groups, respectively). If a Subject in the metal ion cohort becomes symptomatic, this Subject will not be replaced.

### 3.2 Bilateral Subjects

All bilateral subjects will participate in the metal ion sub-study and will follow the blood draw schedule in Table A1 below. The surgery date of the contralateral hip will determine the dates of obtaining blood samples.

In the case of a unilateral subject previously enrolled in the sub-study who requires a contralateral THA, the subject will follow Table A1 based on each THA surgery date. For example, a unilateral sub-study subject has a blood draw at 730 days per protocol. The subject subsequently has a contralateral THA. The subject will now be required to have a blood samples obtained per Table A 1 based on the date of the contralateral THA without regard for the visit schedule of the first enrolled hip. This subject will have a blood draw at 5 years for the first enrolled hip in addition to each of the blood draws listed in Table A1. Thus, unilateral subjects enrolled in the sub-study who subsequently undergo a contralateral THA may have twice as many blood draws during the study as a unilateral, sub-study subject who does not have a contralateral THA.

## 4. Laboratory

Whole blood in Subjects enrolled into the metal ion sub-study will be collected at the Admission, 180 day, 365 day, 720 day, and 5 year follow-up time points. The assessment schedule for the metal ion sub-study can be found in Table A.1.

**Table A 1: Metal-ion sub-study assessment schedule**

| | Screening | Admission | Surgery | Discharge | 42 days ± 7 days | 180 days ± 30 days | 365 days ±60 days | 730 days ±60 days | 3 years ±60 days | 4 years ±60 days | 5 years ±60 days | 6, 7, 8, 9, 10 years | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Metal Ion Sub-Study** | | X | | | | X | X | X | | | X | | |

Blood draw, storage and shipment instructions will be provided to each Investigator participating in the sub-study. Metal ion concentration in whole blood will be measured in the same manner as described in Section 5.6.4 of the main body of the Protocol.

## 5. Analysis of Metal Ion Concentration in Blood

Based on literature data, metal ion concentration in blood has skewed distribution with right tail extreme values. If parametric statistical methods are not appropriate for analysis of these data, the following approach will be used. First, data will be ranked across all follow-ups and Subjects from both Groups. Such rank data will be analyzed using the two-way ANOVA for repeated measurements. Three factors will be analyzed, GROUP (Investigational and Control), TIME and GROUP*TIME interaction. Significant GROUP*TIME interaction will indicate differences in metal ion concentration between the two Groups.

Data on metal ion concentration in symptomatic Subjects will be compared to data in non-symptomatic Subjects using the ANCOVA approach as follows: Non-symptomatic Subjects will

be selected from the sub-study, symptomatic Subjects will include symptomatic Subjects regardless of participation in the sub-study. The closest follow-up visit in the non-symptomatic set will be identified to match the time of the metal-ion blood draw in the symptomatic Subjects and create a single follow-up time observation for the symptomatic and non-symptomatic Subjects. Next all data will be ranked across the Admission and follow-up time point observations and Subjects in both Groups. The ANCOVA model will have one factor (SET; symptomatic and non-symptomatic) and one covariate (baseline metal-ion level observed at the Admission time point). An expanded analysis will be performed to evaluate if possible baseline confounders (e.g. baseline demographics, device size, surgery characteristics, acetabular component position) may impact the findings. Relationship to post-surgery activity levels (e.g. UCLA Activity Scale) and acetabular component migration will also be evaluated. In addition, listings will be provided of symptomatic Subjects and their metal ion values.

## 6. Ethics Approval

IRB/REB/EC/HREC approval of this protocol is inclusive of this sub-study; however, all sites will not participate in the sub-study. The IRB/REB/EC/HREC must be notified of the investigational site's participation in the metal ion sub-study.

# Appendix II – OXINIUM DH Hip System MRI SAFETY INFORMATION

Smith & Nephew, Inc. OXINIUM DH Hip System implants are manufactured from a non-ferromagnetic material, zirconium-niobium alloy. Smith & Nephew has performed non-clinical Magnetic Resonance Imaging (MRI) studies on OXINIUM DH implants which are determined to be MR Conditional in accordance to ASTM F2503-08, Standard Practice for Marking Devices and Other Items for Safety in the Magnetic Resonance Environment. MR Conditional refers to an item that has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use.

**MR Information**

Non-clinical testing has demonstrated that the OXINIUM DH System is MR Conditional. A Subject with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 and 3.0 Tesla only
- Maximum spatial gradient magnetic field of 3,000 gauss/cm (30 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)
- Cylindrical Quadrature transmit coils only


Under the scan conditions defined above, the OXINIUM DH is expected to produce a maximum temperature rise of 10.9 ºC after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extended up to 8.6 cm from the OXINIUM DH system when imaged with a gradient pulse sequence, and up to 7.8 cm from the device when imaged with a spin echo pulse sequence and a 3 Tesla MRI system.

# Appendix III – BIOLOX delta Hip System MRI SAFETY INFORMATION

Smith & Nephew, Inc. BIOLOX◊ delta Hip System implants are manufactured from non-ferromagnetic materials, titanium-aluminum-vanadium alloy, alumina ceramic, and polyethylene plastic. Smith & Nephew has performed non-clinical Magnetic Resonance Imaging (MRI) studies on BIOLOX◊ delta implants which are determined to be MR Conditional in accordance to ASTM F2503-08, Standard Practice for Marking Devices and Other Items for Safety in the Magnetic Resonance Environment. MR Conditional refers to an item that has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use.

**MR Information**

Non-clinical testing has demonstrated that the BIOLOX◊ delta System is MR Conditional. A Subject with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 and 3.0 Tesla only
- Maximum spatial gradient magnetic field of 3,000 gauss/cm (30 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)
- Cylindrical Quadrature transmit coils only


Under the scan conditions defined above, the BIOLOX◊ delta is expected to produce a maximum temperature rise of 10.9 ºC after 15 minutes of continuous scanning.

In non-clinical testing, the image artifact caused by the device extended up to 8.6 cm from the BIOLOX◊ delta system when imaged with a gradient pulse sequence, and up to 7.8 cm from the device when imaged with a spin echo pulse sequence and a 3 Tesla MRI system.

## Appendix IV –Principal Investigator Obligations

1. General:
   a. The role of the PI is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.
   b. The PI is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation (see also 7.6). This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.
2. Qualification of the PI. The PI shall:
   a. be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this International Standard; evidence of such qualifications of the PI and key members of the investigation site team shall be provided to the Sponsor through up-to-date Curriculum Vitae (CV) or other relevant documentation,
   b. be experienced in the field of application and trained in the use of the investigational device under consideration,
   c. disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
   d. be knowledgeable with the method of obtaining informed consent.
3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site:
   a. has the required number of eligible subjects needed within the agreed recruitment period, and;
   b. has an investigation site team that is: qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this document; evidence of such qualifications for members of the investigation site team shall be documented through up-to-date CVs or other relevant documentation;
   c. has adequate facilities.
4. Communication with the IEC. The PI shall:
   a. provide the Sponsor with copies of any clinical-investigation-related communications between the PI and the IEC,
   b. comply with the requirements described in 4.5 of ISO 14155.
      i. Submit to the IEC the following information, any amendments and any additional documentation required by the IEC: The Protocol; IB or equivalent; informed consent form and any other written information provided to subjects; procedures

for recruiting subjects and advertising materials, if any; a copy of the CV of the PI(s) for with the IEC has oversight.

ii. Provide documentation of the IECs approval/favorable opinion, identifying the documents and amendments on which the opinion was based, to the Sponsor, prior to commencing the clinical investigation.

iii. Submit the following to the IEC if required by national regulations, the protocol or IEC, whichever is more stringent:

1. SAEs
2. Requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety, and well-being, or the scientific integrity of the clinical investigation. Document and report to the Sponsor and IEC a report of deviations made to protect the rights, safety, and well-being of human subjects under emergency circumstances.
3. Progress reports, including safety summary and deviations
4. Amendments to any documents already approved by the IEC.
5. If applicable, notifications of suspension or premature termination
6. If applicable, justification and request for resuming the clinical investigation after suspension.
7. Clinical investigation report or summary.

iv. As a minimum, during the clinical investigation, the following information shall be obtained in writing from the IEC prior to implementation:

1. Approval/favorable opinion of amendments
2. Approval of the request for deviations that can affect the subject's rights, safety, and well-being or scientific integrity of the clinical investigation
3. Approval for resumption of a suspended clinical investigation if applicable.

c. obtain the written and dated approval/favorable opinion of the IEC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required,

d. promptly report any deviations from the protocol that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the IEC, protocol or national regulations. In particular circumstances, the communication with the IEC can be performed by the Sponsor, partly or in full, in which case the Sponsor shall keep the Principal Investigator informed.

5. Informed consent process. The PI shall:

a. General:

i. Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject; except when special circumstances for emergency treatments apply (see below)

b. Process of obtaining informed consent. The general process for obtaining informed consent shall be documented in the protocol and shall comply with the following. These requirements also apply with respect to informed consent obtained from a subject's legally authorized representative:
   i. Ensure that the PI or their authorized designee conducts the informed consent process
   ii. Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
   iii. Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
   iv. Not waive or appear to waive the subject's legal rights
   v. Use native non-technical language that is understandable to the subject
   vi. Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
   vii. Include personally dated signatures and the PI or an authorized designee responsible for conducting the informed consent process
   viii. Show how informed consent will be obtained in special circumstances (see below) where the subject is unable to provide him or herself, and
   ix. Ensure important new information is provided to new and existing subjects throughout the clinical investigation.

c. Special circumstances for informed consent (the following provisions are subject to national regulations):
   i. Subject needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within their ability to understand.
   ii. Subject unable to read or write: informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or their legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent for attesting that the information was accurately explained and that the informed consent was freely given.
   iii. Emergency treatments:
      1. For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's

medical condition, the informed consent of the subject's legally authorized representative, if present, shall be requested.

2. When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized representative, is not available, the subject may still be enrolled if a specific process has been described in the protocol.
3. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the clinical investigation and about all aspects of the clinical investigation.
4. The subject shall be asked to provide informed consent for continued participation as soon astheir medical condition allows.

d. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or their legally authorized representative only when the following conditions are fulfilled: the prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation; no sufficient clinical benefits are anticipated from the currently available treatment; there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used; anticipated risks are outweighed by the potential benefits of applying the investigational device ; the legally authorized representative cannot be promptly reached and informed.

e. Information provided to the subject. All information pertinent to the clinical investigation, including at least the following, shall be provided in writing and in native, non-technical language that is understandable to the subject (or the subject's legally authorized representative):

i. Description and purpose
ii. Potential benefits
iii. Risks and inconveniences or the subject and, when applicable, for any embryo, fetus or nursing infant
iv. Alternative procedures
v. Confidentiality
vi. Compensation
vii. Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation
viii. Information on the role of Sponsor's representative in the clinical investigation
ix. Contact persons
x. Statement declaring that new findings or the reasons for any amendment to the protocol that affect the subject's continued participation shall be made available to the subject
xi. Statement indicating that, upon the subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation

xii. Statement indicating that a description of the clinical investigation has or shall be registered in a publicly accessible database
xiii. Termination procedures

f. Informed consent signature shall contain the following:
   i. The voluntary agreement to participate in the clinical investigation and follow the investigator's instructions
   ii. A statement declaring that refusal of participation incurs no penalty for the subject and no loss of benefits to which the subject is otherwise entitled;
   iii. A statement declaring that discontinuation/withdrawal and thereby revoking the informed consent at any time incurs no penalty for the subject;
   iv. A statement with regard to the possible consequences of withdrawal
   v. An acknowledgment of the information provided and confirmation that all the subject's questions were answered that the subject acknowledges the information provided during the informed consent process and that (s)he had ample time to consider participation
   vi. A statement confirming that the subject or their legally authorized representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation
   vii. A statement confirming that the subject or their legally authorized representative agrees that Sponsor's representatives, regulatory authorities and IEC representatives will be granted direct access to the subject's medical records.
g. New information: if new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing consent in writing.
h. ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and
i. ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

6. Compliance with the protocol. The Principal Investigator shall:
   a. indicate their acceptance of the protocol in writing,
   b. conduct the clinical investigation in compliance with the protocol,
   c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits as well as maintain documentation of the type and location of these source documents,
   d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,
   e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device,

f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required,
g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation,
h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports,
k. maintain the device accountability records,
l. Comply with the procedure for the safe return of investigational devices including potentially hazardous devices and, in the case of reported device deficiencies, collaborate with the sponsor to provide the necessary information allowing an accurate analysis where appropriate. requirements and provide any information need to analyze device deficiencies, if applicable.
m. allow and support the Sponsor to perform monitoring and auditing activities,
n. be accessible to the monitor and respond to questions during monitoring visits,
o. determine the cause and implement appropriate corrective and preventative actions to address significant noncompliance,
p. allow and support regulatory authorities and the IEC when performing auditing activities,
q. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and
r. review and sign the clinical investigation report, as applicable.

7. Medical care of subjects. The Principal Investigator shall
   a. provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events,
   b. inform the subject of the nature and possible cause of any adverse events experienced,
   c. provide the subject with the necessary instructions on proper use, handling, storage, and return of the investigational device, when it is used or operated by the subject,
   d. inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,
   e. provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,
   f. ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,

g. if appropriate, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided),
h. inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and
i. make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

8. Safety reporting. The Principal Investigator shall:
   a. record every adverse event and observed device deficiency, together with an assessment,
   b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol,
   c. report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC,
   d. report to regulatory authorities, serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and
   e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

21 CFR Part 812 Investigational Device Exemption Regulations

An investigator shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
2. Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
3. Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
4. Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an

emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.

5. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
6. Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
7. Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

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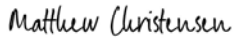
| Matthew Christensen<br>Matthew.Christensen@smith-nephew.com<br>SVP Global Clinical & Medical Affairs<br>Smith & Nephew<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>9CA29354-DDF6-446D-B49D-00024793ADD4<br>Using IP Address: 107.122.189.18<br>Signed using mobile<br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 02-Nov-2023 \| 13:55<br>Viewed: 02-Nov-2023 \| 20:08<br>Signed: 02-Nov-2023 \| 20:09 |
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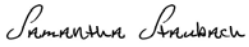
| Samantha Staubach<br>Samantha.Staubach@smith-nephew.com<br>Regulatory Manager 2<br>Smith & Nephew<br>Security Level: Email, Account Authentication (Required), Login with SSO |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>F98C0312-B79E-4658-86DE-CAA76CD4B963<br>Using IP Address: 216.222.219.1<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 02-Nov-2023 \| 13:55<br>Viewed: 10-Nov-2023 \| 01:22<br>Signed: 10-Nov-2023 \| 01:24 |
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| Carbon Copy Events | Status | Timestamp |
|---|---|---|
| Kristin Robinson<br>Kristin.Robinson-CTR@smith-nephew.com<br>Smith & Nephew<br>Security Level: Email, Account Authentication (Required)<br>**Electronic Record and Signature Disclosure:**<br>Not Offered via DocuSign | COPIED | Sent: 02-Nov-2023 \| 13:55 |
| Rebecca McDonald<br>Rebecca.McDonald@smith-nephew.com<br>Clinical Studies Coordinator<br>Smith & Nephew<br>Security Level: Email, Account Authentication (Required)<br>**Electronic Record and Signature Disclosure:**<br>Not Offered via DocuSign | COPIED | Sent: 02-Nov-2023 \| 13:55 |

| Witness Events | Signature | Timestamp |
|---|---|---|

| Notary Events | Signature | Timestamp |
|---|---|---|

| Envelope Summary Events | Status | Timestamps |
|---|---|---|
| Envelope Sent | Hashed/Encrypted | 02-Nov-2023 \| 13:55 |
| Certified Delivered | Security Checked | 10-Nov-2023 \| 01:22 |
| Signing Complete | Security Checked | 10-Nov-2023 \| 01:24 |
| Completed | Security Checked | 10-Nov-2023 \| 01:24 |

| Payment Events | Status | Timestamps |
|---|---|---|