A Consecutive Series Pilot Study Evaluating the Safety and Effectiveness of a New Hard-on-Hard Total Hip Replacement System in Patients with Non-inflammatory Arthritis with a Standard THA Metal Ion Control Group

Protocol Number:	2011-ODHH166
Protocol Date:	Amendment 3, dated 19 January 2017
Study Product Name:	R3 ODH on ODH Hip System
Sponsor:	Smith & Nephew, Inc. 7135 Goodlett Farms Parkway Cordova, TN 38016

Protocol Summary

Title of Study:	A Consecutive Series Pilot Study Evaluating the Safety and Effectiveness of a New Hard-on-Hard Total Hip Replacement System in Patients with Non-inflammatory Arthritis with a Standard THA Metal Ion Control Group
Study Type:	Pilot Study with extension to 10 year follow-up
Investigators:	Mr. Andrew R. Baker (Primary Investigator) Specialist Orthopaedic Surgeon Entabeni Hospital, Durban, South Africa Mr. Ian W. Stead (Co-Investigator) Specialist Orthopaedic Surgeon Entabeni Hospital, Durban, South Africa, Dr. Johan de Beer (Principal Investigator) Specialist Orthopaedic Surgeon Zuid Afrikaans Hospital, Neuro-Ortop. Instituut, Pretoria, South Africa
Endpoints:	Revisions, adverse events and metal ion analysis
Secondary Endpoints:	HHS Score, Radiographic Success, HOOS Questionnaire, and Health Economic Data
Design:	Prospective, consecutive series
Length of Study:	Patients will be followed for 10 years
Number of Centers:	Two centers will participate in the current study
Sample Size (2 year follow up):	25 patients are to be enrolled (20 ODH-ODH/5 control)
Sample Size (10 year follow up):	All patients completing the 2 year primary follow up will be invited to participate in the extension phase of the study

List of Abbreviations

AE	Adverse Event
BMI	Body Mass Index
CoC	Ceramic-on-Ceramic
CoCr	Cobalt chrome
CRF	Case Report Form
CV	Curriculum Vitae
GCP	Good Clinical Practice
GP	General Practitioner
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritis Outcome Scores
IEC	Independent Ethics Committee
ICH	International Conference on Harmonisation
MoM	Metal-on-Metal
ODH	OXINIUM Diffusion Hardened
QOL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
THA	Total Hip Arthroplasty
THR	Total Hip Replacement
UADE	Unanticipated Adverse Device Effect
UHMWPE	Ultra-high molecular weight polyethylene

Study Events Schedule

[a] For Investigational subjects only
[b] Control subjects only
[c] An end of study form will be completed for all subjects at the 10 year visit if not completed prior

Schedule	Preop	Op	DC	3 mo ± 4 wks	6 mo ± 4 wks	1 yr ± 4 wks	2 yr ± 6 wks	5yr -2 wks+ 180 days	6yr ± 90 days	7yr ± 90 days	8yr ± 90 days	9yr ± 90 days	10yr ± 180 days	Unscheduled
Days	-	-	-	64-120	155-211	338-394	689-773	1812 - 2006	2101 - 2281	2466 - 2646	2831 - 3019	3196 - 3376	3471 - 3831	-
Inclusion/Exclusion	√	-	-	-	-	-	-	√	-	-	-	-	-	-
Informed Consent	√	-	-	-	-	-	-	√	-	-	-	-	-	-
Demographics/Med History	√	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Evaluation (HHS)	√[a]	-	-	√[a]	√[a]	√[a]	√[a]	√	-	√	-	-	√	√[a]
Radiography	√[a]	-	√[a]	√[a]	√[a]	√[a]	√[a]	√		√			√	√
Metal Ion Testing (Whole Blood)	√	-	-	√	√	√	√	√	-	√	-	-	√	√
HOOS Subject Questionnaire	√[a]	-	-	√[a]	√[a]	√[a]	√[a]	√	-	√	-	-	√	√[a]
Adverse Events	-	√	√	√	√	√	√	√	√	√	√	√	√	√
End of Study	-	-	-	-	-	-	-	-	-	-	-	-	√[c]	-
Retrospective Demographics/Med History Data Collection[b]	√	√	√	√	√	√	√	-	-	-	-	-	-	-
Retrospective Clinical Evaluation (HHS)[b]	√			√	√	√	√							
Retrospective HOOS[b]	√			√	√	√	√							
Retrospective Adverse Event Data Collection[b]	√	√	√	√	√	√	√	-	-	-	-	-	-	-
Retrospective Radiography Data Collection[b]	√	√	√	√	√	√	√	-	-	-	-	-	-	-

Table of Contents

1.0 Background and Purpose

The primary purpose of this study is to collect safety data on revisions, peri/post-operative adverse events related to either the device or the surgical procedure, and metal ion analysis of [redacted] (ODH) components using the ODH on ODH Hip System to evaluate a new hard-on-hard total hip replacement (THR) system [redacted] Additionally, efficacy data will be collected; HHS, HOOS and radiographs.

The intended use of R3 ODH-ODH is for patients with hip disease requiring primary THR.

10 Year Extension Study

The purpose of the 10 year extension study is to assess the long term safety and efficacy of the R3 ODH-ODH Hip System in patients with hip disease requiring primary THR.

Hard-on-Soft Bearings

The classic bearing coupling in THR is a hard femoral head articulating against a relatively soft ultra-high molecular weight polyethylene (UHMWPE) acetabular liner. This hard-on-soft articulation has long served as the gold standard in THR, allowing for excellent clinical outcomes (Ries, 2005). However, wear of UHMWPE liners has been a significant concern, as generation of particle debris has been shown to significantly increase periprosthetic osteolysis (Allen and Beaule, 2008). The resistance of UHMWPE to wear and oxidation can be significantly increased through cross-linking (Digas et al, 2007; Triclot et al, 2007).

Here, UHMWPE is exposed to a dose of ionizing irradiation, or heat treatment above or below melting point (annealing and remelting, respectively). This induces the breakdown or unwinding of polyethylene chains and the resulting cross-linking of adjacent chains. While performance is greatly improved, wear of cross-linked UHMWPE does still occur (Garvin et al, 2009). Additional methods of improving UHMWPE wear, including carbon reinforcement and high crystallinity, were initially promising but have not proven clinically successful (Pryor et al, 1992; Taeger et al, 2003).

Femoral head choice can also significantly affect clinical outcomes in hard-on-soft bearing couplings. Cobalt chrome (CoCr) heads are highly durable and resistant to fracture, but can cause relatively high wear due to abrasion (Bal et al, 2007; Bourne et al, 2005; Good et al, 2003). Alternatively, ceramic heads offer improved hardness, wettability, and are less prone to abrasive scratching (Kusaba and Kuroki, 1997). However, ceramics are inherently brittle and can fracture in vivo (Lang et al, 2008). In order to address these issues Oxidized Zirconium (OXINIUM™, Smith & Nephew, Inc., Memphis, TN, USA; OX) was developed to overcome the relative material limitations of existing femoral heads.

While the performance of hard-soft couplings has significantly improved with the advent of advanced bearing surfaces, polyethylene wear remains a concern. Wear rates may also potentially increase when larger femoral heads are coupled with polyethylene. The benefits of larger femoral head sizes include decreasing dislocation risk and improving early functional outcomes (Skeels et al, 2009; Zhou et al, 2009; However, the use of larger head sizes limits polyethylene thickness, potentially increasing wear and failure risk (Lachiewicz et al, 2009).

Hard-on-Hard Bearings

The limitations of hard-soft couplings are mitigated through the use of hard-on-hard bearings. Here, CoCr and ceramic femoral heads are paired with CoCr or ceramic acetabular liners. First generation CoCr-on-CoCr, or metal-on-metal (MoM) designs, were introduced in the 1960's (Manley and Sutton, 2008), while ceramic-on-ceramic (CoC) designs first appeared during the 1970's (Hamadouche et al, 2002). These bearing couplings have been shown to support excellent clinical outcomes and relatively low wear rates (Manley and Sutton, 2008). However, hard-on-hard bearings are not without risk. There remains concern that, despite material advances, ceramics may still be susceptible to fracture (Hamilton et al, 2010). While polyethylene wear is no longer a concern with metal hard-on-hard bearings, the release of metal ions may result in a new safety and efficacy concern. Specifically, patients may experience periprosthetic hypersensitivity to elevated nickel (Ni), chromium (Cr) or cobalt (Co) ion levels. Ion elevation has been associated with increased risk of adverse reactions, such as pseudotumor development (Kwon et al, 2010). These reactions have been hypothesized to lead to early failure in THR (Deprez et al, 2010).

Based upon its wear and fracture resistant characteristics, oxidized zirconium appears to be appropriate for hard-on-hard bearings. This is especially true when considering metal ion release. It is estimated that upwards of 15% of the population may be hyper-sensitive to metal ions (Basketter et al, 1993).

[redacted] Available evidence supports improved wear characteristics of OX (Bourne et al, 2005; Mazzucco and Spector, 2004; Good et al, 2003). Moreover, early clinical evidence supports improved wear of OX in vivo (Haddad et al, 2010).

Within this population, Hallab et al (2004) and Hallab et al (2001) note that Ni is the most common metal sensitizer, followed by Co and Cr. These hypersensitive responses are largely characterized by an elevated immune response commonly associated with clinical complication (Hallab et al (2001). [redacted]

While highly effective for hard-on-soft bearings, OXINIUM devices may not be durable enough for hard-on-hard applications. As a result, a new version of OXINIUM has been developed.

[redacted]

Preclinical research has been performed to assess the safety of ODH. This is outlined in detail in the Investigator's Brochure.

The primary purpose of the pilot study was to determine early safety and efficacy results post-operatively at six months for R3 ODH-ODH couplings in THR. The purpose of the additional follow-up through 10 years post-implantation is to assess the long term safety and efficacy of the R3 ODH-ODH Hip System in patients with hip disease requiring primary THR.

2.0 Study Summary

2 Year Primary Study

- The purpose of the investigation is to assess the early safety and efficacy of R3 ODH-ODH utilization during primary THR.
- This is a prospective, consecutive series, non-randomized, multi-center clinical study.
- Twenty (20) patients are to be enrolled in the current study, with 5 THA control subjects for metal ion analysis.
- This study is to be executed according to ICH GCP guidelines for clinical trials and in accordance with the Declaration of Helsinki.
- Patients will be followed-up for two (2) years post-operatively.
- Interim analyses will be conducted post-operatively at six (6) months and a full study report will be generated at two (2) years.

10 Year Extension Study

- The purpose of the additional follow-up through 10 years post-implantation is to assess the long term safety and efficacy of R3 ODH-ODH utilization during primary THR.

- Both investigational and control subjects will be invited to participate and sign an updated Informed Consent Form if agreeable.
- Subjects from the original control group will be invited to participate in retrospective collection of secondary endpoint data as this was not originally collected in the 2 year primary study. This data includes adverse event data, radiography, HOOS, HHS, demographic and medical history data if available. If agreeable, they will be asked to provide written Informed Consent.
- Control subjects who do not wish to participate in the extension phase may still consent to the retrospective data collection from their medical files. Similarly, control subjects who do not wish to consent to the retrospective collection of data from their medical files may still participate in the extension phase of the study.
- This extension study is to be executed according to ICH GCP guidelines for clinical trials and in accordance with the Declaration of Helsinki.
- Subjects will be followed for 10 years post-operatively.
- Interim analyses will be conducted post-operatively after all subjects have completed 5 year and 7 years visits. A complete study report will be completed when all subjects have completed the 10 year follow-up.

3.0 Outcome Measures

3.1 Primary Outcome Measures

- Primary safety will be assessed by the incidence of device related revision, adverse events and metal ion measurements.
- Adverse events will be documented at the intraoperative and all post-operative evaluation intervals. The incidence of surgery-related and device-related events such as squeaking, liner fracture, device revision, malfunction, migration, subluxation, dislocation, loosening, nerve damage, deep infection, deep vein thrombosis, pulmonary embolism, or bone breakage/fracture will also be collected. Any adverse events with an unknown association with the surgery or device will also be collected.
- For both investigational and control subjects, metal ions will be measured in whole blood, including Co, Cr, Ni, Ti, Zr, Nb, Mo, V and aluminum (Al) ion levels, preoperatively, 3 month, 6 month, 1 year, 2 years, 5 years, 7 years and 10 years post-operatively.

3.2 Secondary Outcome Measures

- The Harris Hip Score (Harris, 1969; HHS) and Hip Disability and Osteoarthritis Outcome Scores (HOOS) will be calculated preoperatively and at the 3 month, 6 month, 1 year, 2 year, 5 year, 7 year and 10 year post-operative follow-up visits for investigational subjects.

  The HHS score, which ranges from 0 (worst) to 100 (best), considers information on pain, function, and range of motion. The HOOS questionnaire captures health-related quality of life data.

HOOS and HHS will be collected retrospectively (if the subject provides consent and the scores are available) for subjects from the original control group.

- Radiographic success includes the assessment of bone loss, radiolucencies, subsidence, and heterotopic ossification as compared to the preoperative radiograph.

- The following health economic data elements will be collected:
  - Surgical blood loss
  - Length of hospital stay
  - Operative time
  - Adverse events (complications)
  - Re-hospitalizations
  - Functional outcomes using the Harris Hip Score

4.0 Device Description

In the R3 ODH-ODH System, ODH femoral heads will be coupled with 12/14 taper ANTHOLOGY and SYNERGY femoral stems (Smith & Nephew, Inc., Memphis, TN, USA). ODH liners will be coupled with R3™ acetabular cups (Smith & Nephew, Inc., Memphis, TN, USA). [redacted]

All enrolled subjects will receive the R3 acetabular cup, and an uncemented SYNERGY or ANTHOLOGY femoral stem.

4.1 R3 ODH-ODH Components

The R3 ODH-ODH study components include:

- R3 ODH acetabular cup liners (sizes 38/50, 40/52, 42/54 and 44/56 mm)
- R3 ODH femoral heads (sizes 38, 40, 42 and 44 mm)
- R3 uncemented cups (sizes 50, 52, 54 and 56 mm OD)
- Taper sleeves Ti -6AL-4V (sizes -4, +0, +4, and +8)
- Uncemented ANTHOLOGY and SYNERGY Smith and Nephew femoral stems

4.2 Control Components

- The commercially available R3 cups, OXINIUM heads on polyethylene liners or ceramic heads on ceramic liners (all uncemented components) will be used in the control subjects
- Uncemented ANTHOLOGY and SYNERGY Smith and Nephew femoral stems.

4.3 Inventory Control

Only qualified Investigators participating in the current study will receive investigational product. The investigational device inventory is shipped directly to a qualified, study Investigator. The Investigator is responsible for adequate record keeping regarding receipt, use, and return of inventory. A “Device Tracking Log” will be provided to each Investigator. Additionally, each Investigator participating in this study must be able to store investigational devices in a controlled access manner (locked storage case) within their operating hospital. This space must be separate from other inventory, and accessible only to the Investigator or study designee. Oversight of device tracking and any necessary reconciliation will be performed by the Investigator and monitored either by the Sponsor or by a contract research organization (CRO) on behalf of the Sponsor.

4.4 Surgical Technique

All hip replacement procedures for R3 ODH-ODH will be performed according to the R3 ODH-ODH surgical technique. A surgical technique brochure for implanting all components will be provided to each Investigator.

5.0 Consecutive Enrollment and Subject Selection

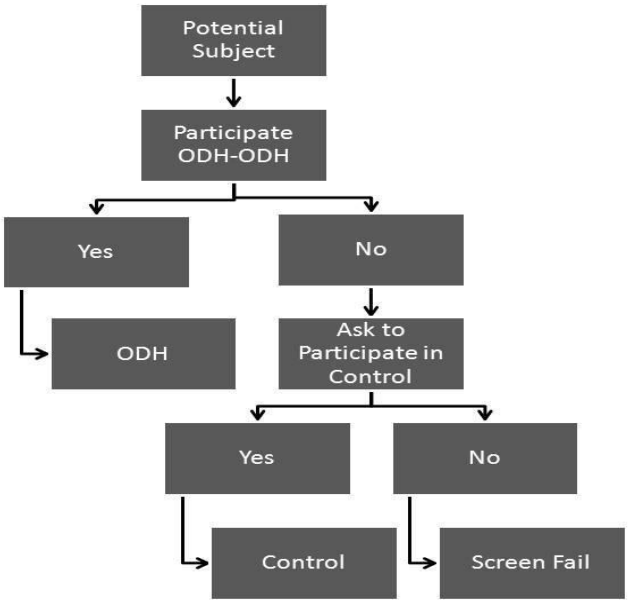
This clinical study of the R3 ODH-ODH total hip system can fulfill its objectives only if appropriate subjects are enrolled. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable. All subjects who meet inclusion/exclusion criteria should be invited to participate in the clinical study to ensure there is no patient selection bias. Documentation of screening efforts should be maintained, with reasons noted for exclusion or denial to participate.

1. All THA candidates meeting the inclusion/exclusion criteria below will be asked to participate in the study (2 Year Primary Study)

2. Subjects who refuse ODH-ODH enrollment will be asked to participate in the control group. (2 Year Primary Study)

3. All subjects meeting the inclusion/exclusion criteria for the 10 year extension study will be asked to participate in the study (10 Year Extension Study)

2 Year Primary Study - The enrollment procedure is outlined below:



5.1 Inclusion Criteria

2 Year Primary Study

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

- Subject is at least 21 years of age
- Subject is skeletally mature
- Subject requires primary, unilateral total hip arthroplasty, due to degenerative joint disease
- Subject has a preoperative Harris Hip Score of ≤ 70
- Subject has met an acceptable preoperative medical clearance and is free or treated for cardiac, pulmonary, hematological, or other conditions that would pose excessive operative risk
- 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 able to fully understand the purpose of the study, his/her role as a participant in the study, and plans to be available through two years post-operative follow-up

10 Year Extension Study

- Subject has completed the 2 year primary study

- Subject has signed an Independent Ethics Committee (IEC) approved Informed Consent Form agreeing to participate in the extension study after the nature, scope and possible consequences of the study have been explained in an understandable form
- Subject is able to fully understand the purpose of the study, his/her role as a participant in the study, and plans to be available through ten years post-operative follow-up

5.2 Exclusion Criteria

2 Year Primary Study

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

- Subjects with diagnosis known to be of high risk for failure of THA
- Subject requires bilateral THR
- Subject requires revision of a prior hip replacement
- Subject has active infection or sepsis (treated or untreated)
- Subject has history of local hip infection
- Subject has presence of known metastatic or neoplastic disease
- Subject has conditions that may interfere with the THA survival or outcome (e.g. , Paget's or Charcot's disease, vascular insufficiency, muscular atrophy, uncontrolled diabetes, or neuromuscular disease)
- Subject has need for structural bone grafts to support the implant
- Subject has contralateral lower extremity condition causing abnormal ambulation and noncompliance with rehabilitation
- Subject has other joint replacements, or plans for other joint replacement surgeries in the next 2 years
- Subject has had systemic steroid therapy within 3 months prior to surgery
- Subject has life expectancy less than 2 years
- Subject has had drug therapy for the index hip with intra-articular corticosteroid therapy or intra-articular hyaluronic acid therapy (or any other intra-articular therapy) within 6 months of enrollment into the study
- Female subject of child-bearing age not using an approved method of contraception
- Subject has inadequate bone stock to support the device (severe osteopenia, family history of severe osteoporosis or osteopenia)
- Subject has known moderate to severe renal insufficiency
- Subject has an emotional or neurological condition that would pre-empt their ability or unwillingness to participate in the study including mental illness, mental retardation, or drug, alcohol abuse
- Subject is severely overweight (BMI>40)
- Above knee amputation of the contralateral and or ipsilateral leg
- Known allergies to any components of the devices
- Subject is entered in another investigational drug, biologic, or device study

- Subject is a prisoner

10 Year Extension Study

- In the opinion of the surgeon, the subject's health, safety or well-being may be compromised or harmed by continuation in the extension phase or participation may not be in the subject's best interests.

6.0 Independent Ethics Review

Investigators are responsible for obtaining written and dated approval from an IEC prior to initiating a study. This approval should include the protocol, the informed consent form, subject recruitment materials, advertising or any written information that will be provided to patients. Copies of the written and dated approvals must be provided to the Sponsor prior to the shipment of the device.

The Sponsor reserves the right to review the IEC application and informed consent form prior to submission as it relates to the Sponsor's obligations.

Investigators are responsible for maintaining IEC approval throughout the study by submitting progress reports (continuing review reports) at least annually and more often if requested by the IEC.

Additional documents that require the Investigator obtain written and dated IEC approval during the course of the study include:

- Protocol amendments (should not be implemented prior to IEC approval)
- Informed consent form revisions (Sponsor reserves the right to review all revised informed consent forms prior to submission as they relate to the Sponsor's obligations
- Protocol deviation reports
- Adverse events, as described in this protocol
- All other documents as required by the IEC

Investigator will provide a closeout report to the IEC and the Sponsor on completion of the study.

7.0 Informed Consent

Investigators are responsible for obtaining and documenting the voluntary informed consent of the study subjects prior to conducting any study-related assessments per ICH E6 GCP. The informed consent form should include all elements noted in the GCP guidelines. The Sponsor reserves the right to review and approve the informed consent form as it relates to the Sponsor's obligations to the subjects.

When obtaining informed consent, Investigators must adhere to ICH E6 GCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to

beginning the study the Investigator must obtain written and dated approval of the informed consent form from the IEC.

The study and informed consent form should be fully discussed with the subject. The subject must be allowed adequate time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject. If the subject agrees to participate, the subject must sign and personally date the consent form in the presence of the Investigator or the Investigator's designee conducting the informed consent discussion, who must also sign and personally date the consent form. Subjects should receive a copy of the initial signed and dated informed consent form prior to the subjects' participation in the study

The informed consent process must be fully documented in the medical record, including notations that (1) adequate time to consider participation was provided to the subject, (2) all questions were answered to the satisfaction of the patient, (3) informed consent was obtained prior to all study procedures. Two (2) copies of the signed and dated, fully executed consent form are to be made. The original must be filed in the site master file, one copy given to the participant to keep and one copy must be filed with the participant's source notes/medical file. The informed consent form and any other written information provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's continued consent. All revised informed consent forms must have written and dated IEC approval in advance of use. The same procedures noted above regarding initial informed consent must be followed for all subsequent consent revisions. It is very important that the appropriate and most recent version of the Informed Consent Form be presented to subjects.

2 Year Primary Study

For the 2 year primary study, separate consent forms will be provided and signed by the subjects depending on which arm the subject is enrolled to.

10 Year Extension Study

For both arms, the re-consenting of all subjects will be done using a unique Informed Consent Form. In addition, for the 10 year extension study, subjects should also indicate on the Informed Consent Form whether they would like to have their family doctor or General Practitioner (GP) informed of their participation should they agree and/or contacted at the end of the study should the study site lose contact with the subject. The study surgeon/staff may only contact the subject's family doctor if the subject has NOT withdrawn consent.

In the case where the subject is unable to read and/or write at least one impartial witness should be present during the informed consent discussion. The impartial witness must read and personally sign and date the Informed Consent Form. A reason e.g. illiteracy for the participant not being able to personally sign and date the Informed Consent Form must be documented in the in the source notes.

8.0 Prior to Study Initiation

The following documentation must be sent to Smith & Nephew prior to initiating the study. These documents will be verified at specified time points for their validity.

- Copies of IEC approval documents for the study protocol and informed consent
- Good Clinical Practice (GCP) training records
- The signed Statement of Investigator or Declaration by Trialist in which the Investigator agrees to conduct the study in accordance with the approved study protocol, ICH GCP (E6) Guidelines, IEC and regulatory requirements, and Sponsor requirements
- A current, signed, dated CV and medical license for each Investigator documenting the location where the study will be conducted
- A completed financial disclosure of any conflict of interest

9.0 Screening Procedures

Investigators and their employees may use or disclose protected health information to aid study recruitment per local regulations.

However, Investigators or their employees should not disclose patient information to others such as the Sponsor or its agents without authorization. The Investigator may use protected health information to contact prospective research subjects for purposes of obtaining authorization to disclose information and/or to discuss the option of enrolling in a clinical study.

Protected health information for subjects who decline to participate in the study should not be provided to the Sponsor or its agents except in a de-identified format such as a screening log without patient identifiers.

10.0 Preoperative Procedures

Informed consent must be obtained prior to conducting any and all study-related assessments *except where data may be obtained from routine care assessments as noted below:*

- Inclusion and exclusion criteria will be carefully reviewed.
- Demographic and medical history information will be obtained at the preoperative visit for investigational subjects and retrospectively for control subjects.
- The clinical evaluation will be completed assessing each element of the HHS. If a complete HHS was performed up to 60 days prior to informed consent, it may be used for the preoperative HHS assessment. Please note that if using a routine care HHS, all elements must be completed at one time-point and the individual elements may not be completed at different time-points. If the HHS is not routine care, it must be performed after consent at the preoperative visit for investigational subjects. HHS data will be collected retrospectively for control subjects if available
- Initial AP and lateral radiographs will be obtained. Copies will be provided to the

Sponsor for the purpose of obtaining independent radiographic analysis. X-rays completed up to 60 days prior to informed consent may be used for the preoperative x-ray. If the x-ray was not completed as routine care within 60 days prior to consent it must performed after consent at the preoperative visit for investigational subjects. Radiographic data will be collected retrospectively for control subjects if available.

- Collection of whole blood samples will occur for the purpose of obtaining baseline metal ion levels. This analysis will be completed at a central laboratory selected by the Sponsor.
- Completion of HOOS subject questionnaire will occur at the preoperative visit for investigational subjects. The HOOS questionnaire should not be mailed to the patient and should be completed during the visit entirely by the investigational patient. A qualified member of study team should confirm if all questions are answered, and if not, should determine if the question was inadvertently missed or if the subject does not want to answer the question. This should be documented in the source document. HOOS data will be collected retrospectively for control subjects if available.

11.0 Operative/Discharge Procedures

- Information on the operative procedure for each subject including surgical approach, component catalog numbers, component size, surgical time, blood loss and other health economic data will be obtained from the medical records at the time of surgery for investigational subjects and retrospectively for control subjects if available.
- All operative complications, both intraoperative and post-operative through discharge will be collected at the time of surgery for investigational subjects and retrospectively for control subjects if available. Any complication device-related, surgery related or otherwise will be collected and reported where applicable.
- Radiographs will be obtained prior to discharge. If radiographs cannot be obtained at discharge they may be obtained within six weeks post-surgery for investigational subjects. Radiographic data obtained at the standard-of-care time points for control subjects should be collected retrospectively if available.

12.0 Metal Ion Analysis

Metal ions will be measured in whole blood and analysis performed by a central laboratory. In order to control for variations in ion measurements, both the control group and the investigational group will undergo the same metal ion analysis described in this section. The pre-op ion measurements will serve as a control for change in Zr ions (and other ions as well) from pre-op to post op time points. However, there is extremely limited data on Zr levels in patients undergoing Total Joint Arthroplasty. Additionally, it is easy to contaminate samples with Zr either during draw or at the analytical facility which could lead to misleading results. In order to understand this potential source of contamination or analytical error, it is necessary to draw blood from the control group. This will give information on background levels of Zr during that time point and thus will avoid any time trends associated with the analytical technique and blood draw. Furthermore, it is not

known how vitamin supplementation affects metal ion readings in whole blood. So having a non-zirconium device will provide "background data" for Zr in patients undergoing THA.

Samples will be collected and shipped preoperatively, 3 months, 6 months, 1, 2, 5, 7 and 10 years post-operatively. Metal ions to be analyzed will include: cobalt (Co), chromium (Cr), nickel (Ni), titanium (Ti), zirconium (Zr), niobium (Nb), molybdenum (Mo), vanadium (V) and aluminum (Al) ion levels. Patient's with blood cobalt or chromium levels greater than 7 parts per billion (ppb), or patients with other ion levels felt to be higher than what is considered normal, will require a second metal ion level to be performed three months after the first high level is identified. If the ions continue to show elevation over normal, cross sectional imaging (MRI or ultrasound) should be done. If the imaging results show soft tissue reactions, fluid collections or tissue masses then a revision surgery should be considered (MDA/2010/033).

13.0 Device Replacement/Bail - Out Procedure

If a device replacement is necessary or required during the surgery, the reason for device replacement or bail out must be clearly documented in the patient record, and on the Adverse Event CRF. Participants that are terminated from the study as a result of the device replacement will continue to receive follow-up care by their surgeon as standard of care practice. No additional follow-up will be conducted for the purposes of the study.

14.0 Post-operative Procedures

Subjects will be seen post-operatively at the 3 month, 6 month, 1, 2, 5, 7 and 10 year intervals, post-surgery. At the discretion of the Sponsor, additional unscheduled follow-up visits may be performed. Information regarding interval specific study events may be found in the Study Events Schedule.

Post-operative procedures include:

- Revision status
- Assessment of adverse events
- Collection of whole blood samples for metal ion analysis at the 3 month, 6 month, 1, 2, 5, 7 and 10 year intervals.
- Telephonic assessment of adverse events at 6, 8 and 9 year intervals.
- A clinical evaluation will be completed by the Investigator for purposes of completing the HHS for investigational subjects at the 3 month, 6 month, 1 and 2 year intervals. Any HHS data available for control subjects will be collected retrospectively up until 2 years post-op. From the 5 year interval onwards (5,7 and 10 year intervals) HHS will be collected prospectively for all subjects.
- AP and lateral radiographs will be obtained. Copies will be provided to the Sponsor for the purpose of obtaining independent radiographic analysis for investigational subjects. Any radiographic data available for control subjects will be collected retrospectively up until 2 years post-op. From the 5 year interval onwards all

radiographic data will be collected prospectively.

- Completion of HOOS subject questionnaire for investigational subjects at the 3 month, 6 month, 1 and 2 year intervals Any HOOS data available for control subjects will be collected retrospectively up until 2 years post-op. From the 5 year interval onwards (5,7 and 10 year intervals) HOOS will be collected prospectively for all subjects.

15.0 Subject Withdrawals

Study participation is voluntary and subjects may withdraw at any point and for any reason during the study. A final evaluation will be completed for all subjects who do not finish the study, and the reason for the withdrawal will be documented in the source documentation and on the appropriate case report form (CRF).

The Investigator may withdraw subjects from the study for any of the following reasons:

- Serious adverse event that precludes continued participation
- Investigator's decision to withdraw subject
- Subject does not receive study device during surgery
- Subject noncompliant with visits
- Subject lost to follow-up

Reasonable efforts to keep each subject in the study should be made and these efforts should be documented by the Investigator. Although the subject is not obligated to give his/her reason(s) for withdrawing prematurely from the study follow-up procedures, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

16.0 Lost to Follow-up

A subject will be considered lost to follow-up if he/she does not appear for a scheduled study visit and study personnel are unable to contact the subject. Study personnel must make a reasonable effort to contact the subject and document a minimum of three contact attempts prior to declaring a subject to be lost to follow-up. Copies of all attempts to reach the subjects per regular mail or email and/or the attempts to contact the subject via other means should be documented and that documentation should be kept with the patient's CRF. An End of Study CRF should also be completed.

If a subject grants permission on the Informed Consent Form to have their family doctor/GP contacted, the study surgeon/staff may contact the subject's family doctor/GP to ascertain the overall status of the subject's health. The study surgeon/staff may only contact the subject's family doctor/GP if the subject has provided consent to do so and has NOT withdrawn consent from the study. The contact with the family doctor should be recorded in the source documentation.

17.0 Safety reporting

All operative complications, both intraoperative and post-operative through discharge will be collected at the time of surgery for investigational subjects and if available collected retrospectively for control subjects.

Any complication, other study hip device-related adverse events, surgery related or otherwise will be collected through to study completion and reported on the appropriate CRF, according to the definitions in the following section.

17.1 Definitions for safety reporting

A. Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (ISO 14155:2011).

This definition includes:

- events related to the investigational medical device or the comparator
- events related to the procedures involved
- a worsening of any conditions previously recorded as part of the medical history assessment

For users or other persons, this definition is restricted to events related to investigational medical devices.

B. Serious Adverse Event (SAE)

A SAE is an adverse event that (ISO 14155:2011):

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- led to foetal distress, foetal death or a congenital abnormality or birth defect

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

C. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device (ISO 14155:2011).

This definition includes:

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

D. Serious Adverse Device Effect (SADE)

An SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (ISO 14155:2011).

E. Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or the clinical investigation plan (ISO 14155:2011, 21 CFR 812).

F. Device Deficiency

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

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

G. Revisions

A specially designed Revision Case Report Form will be used in addition to the Adverse Event Form, to document in detail revisions of any of the components of the study device.

17.2 Safety: Investigator's Responsibilities

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

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

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

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

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

17.3 Timelines for Submission of Safety Information:
The timelines begin when the Investigator becomes aware of the event.

The Investigator will report to the Sponsor:

- As soon as possible, but no greater than **24 hours upon becoming aware of the event, SAEs*, SADEs, U(S)ADEs and device deficiencies that could have led to a SADE**:
  - if suitable action had not been taken
  - if intervention had not been made, or
  - if circumstances had been less fortunate
- **Revisions**, **within 24 hours upon becoming aware of the event.** Sponsor will provide an explant retrieval kit on becoming aware of a revision and ask the Investigator to return any revised components for retrieval analysis.

* SAEs which do not require reporting within 3 calendar days can be listed in the clinical investigation plan[3].

Investigators may also be asked to supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

The Principal Investigator will be responsible for reporting to the IRB/EC of the study site and to the regulatory authorities, SAEs, SADEs and device deficiencies that could have led to a SADE, as required by the national regulations.

17.4 Safety reporting: Sponsor's Responsibilities

Sponsor will provide progress reports on safety events to the Investigator to report to the IRB/EC as required.

In the case of multicenter studies, Sponsor will inform all Investigators in writing of all SAEs that were reported by all sites throughout the clinical investigation and based on perceived risk.

The Sponsor will also, in case of SADEs and device deficiencies that could have led to SADEs, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

18.0 Device Failure leading to revision

In the short term, THA failure can occur due to infection, dislocation, instability, and/or subject experiencing severe pain due to various causes. Reduced mobility alone, is typically not a predominant factor in prompting revision surgery. In the longer-term, aseptic loosening and/or severe pain may become a determining factor as to whether to proceed with device revision. Reasons for removal are not limited to these circumstances alone.

The Sponsor should be notified immediately when a revision is planned. The Sponsor or its designee will provide an explant retrieval kit and the site will return any revised components for retrieval analysis according to provided instructions. Any explanted 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 taken prior to the revision procedure as per an unscheduled visit on the study visit schedule. Patients who have undergone revision surgery will be withdrawn from the study and no additional follow-up visits will occur.

Explanted components are to be sterilized by steam autoclave or other appropriate sterilization method according to the Institution's standard sterilization procedures. Only properly packaged explants should be shipped, and the Sponsor notified before any shipment. If possible, the Sponsor will collect histological (bony in-growth quality, bone quality, response to potential wear debris, etc.) and metallurgical (metal wear, deformation, cracking, corrosion, etc.) information from explants, and this information will be reported in annual safety reports. For all explants, the Investigator must record and forward a description of intra-operative findings including: 1) presence of wear debris, 2) what types of components are being replaced, 3) and intraoperative findings relating to the device failure. It should be noted that the Sponsor is not always able to retrieve known explants.

19.0 Case Report Forms

Case report forms (CRFs) will be used to collect the data obtained during this study. A complete set of CRFs will be provided for each subject enrolled. Data will be submitted by the Investigators to Smith & Nephew, Inc. for computer compilation.

Smith & Nephew, Inc. currently uses the DataFax data collection system. It allows for case report forms to be faxed directly into the database system. Using this system will increase the speed and efficiency of data collection from the study sites, and will improve the quality of the study data through the use of automated data queries. DataFax will also track subject visits according to the scheduled intervals. Periodic due/overdue reports will be sent to the clinical site to help ensure subjects are evaluated at the appropriate intervals.

Investigators are responsible for ensuring that all data are accurately completed on the CRFs. Any parameters not collected may adversely impact the quality and validity of the final results of this study. Special care should be taken to record any device or surgery-related adverse events including a complete description of their relationship to the study device. Adverse event CRFs should be signed by the Investigator.

Quality assurance procedures are designed to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that Adverse Events are immediately identified and addressed until closure.

Global Clinical Operations at Smith & Nephew, Inc. will promptly review all faxed CRFs and accompanying documentation to identify inconsistent or missing data and device-related complications. Problems with these data will be addressed via electronic queries. To ensure the confidentiality of data, Smith & Nephew, Inc. will maintain a secure study database.

20.0 Source Documents

Investigators are responsible for obtaining and maintaining complete patient health information in the medical record for each subject and each assessment (source documents). Source data includes all information in original records and certified copies of original records of clinic findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (e.g., hospital records, clinic and office charts, memoranda, dispensing records, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection and shipment records, research subject files, etc.) Data found in the CRF and submitted to the Sponsor must have a corresponding source document in the patient record(s) that provides detailed evidence of the assessment.

The Sponsor and its agents will be provided direct access to source documents for the purpose of verifying and evaluating the clinical data submitted to the Sponsor by the Investigator on CRFs.

21.0 Completion of Study

The Investigator is expected to complete enrolment and follow-up per the protocol and clinical trial agreement. Continuation of this study beyond the agreement must be mutually agreed upon in writing both by the Investigator and by the Sponsor.

22.0 Statistical Analysis

22.1 Study Design

The objective of this study is evaluating the safety and effectiveness of the R3 ODH-ODH primary THR system with a Standard THA Metal Ion Control Group. The primary outcomes will be revision, study hip adverse events, and metal ion analysis at the 6 month time-point, at the 2 year time-point, and again at the 7 and 10 year time-points. The metal ion results of the five control subjects will be compared to those of the 20 ODH subjects in order to validate the metal ion levels in the ODH population. The results at the 6 month time-point will be used to meet the safety committee's requirements for early clinical data to support safety. The focus of the 5 year analysis will be on safety and efficacy. An additional interim analysis will be conducted at 7 years and the final report will be performed at 10 years.

22.2 Sample Size

A total of 25 subjects will be enrolled (20 ODH-ODH and 5 controls) in the study and all must reach their 6 month follow-up interval.

22.3 Statistical Analysis

22.3.1 Analysis of Population

2 years Primary Study Analysis

The primary analysis will be comprised of all patients who have completed the 6 month post-operative follow-up visit. Twenty-Five patients who have completed the 6 month visit are needed to complete the primary interim analysis and the metal ion analysis will compare to control subjects. A final analysis which will include efficacy assessments will be completed at the 2 year time point. All subjects who do not complete the study, for reasons other than device failure, will be described in the final analysis.

The control subjects will ONLY be asked for blood samples and no other study assessments will be required. Therefore, they will not be included in the over-all analysis. The metal ion results of the five control subjects will be compared to those

of the 20 ODH subjects in order to validate the metal ion levels in the ODH population.

5, 7 and 10 year Study Analyses

The extension study will be comprised of all subjects who have completed the 5 year, 7 year and 10 year post-operative follow-up visits. The analyses will include the descriptive statistics in both safety and efficacy variables. All the data collected during the study will be presented as tables or listing.

22.3.2 Primary Analysis Objectives

The primary interim analysis will assess feasibility of this new hard-on-hard construct using safety data. Data points of interest include Metal Ion Analysis, occurrence of serious device related adverse events, and revision.

22.3.3 General Statistical Methods

Appropriate summary statistics will be calculated and reported to describe the overall study results. Confidence intervals will be calculated as needed to assess the degree of precision in estimates. Approximate significance (α) levels of 5% will be used in statistical tests and confidence intervals.

Data tabulations and summarization will be presented to aid in the interpretation of the effects of clinically significant variables that are disclosed. Summary of continuous variables will be summarized using mean, SD, minimum, and maximum; categorical variables will be summarized as counts and percentages.

Appropriate parametric and/or non-parametric analyses will be chosen for statistical analysis. Test of association for the table of counts will be based on the Fisher's Exact Test unless otherwise noted.

Continuous variables will be analyzed using t-test and ANOVA if appropriate. Otherwise, the hypothesis of location for these measurements will be tested using Wilcoxon rank-sum or Kruskal-Wallis tests.

Time course distribution of Adverse Events for the safety population will be tabulated. Analysis of revision status will be using test of proportion such as Binomial test and Fisher's Exact test unless otherwise inappropriate.

A listing will be created to present all the data collected during the study.

22.3.4 Missing Data

A Patient accountability table, along with the explanation for lost-to-follow-up, death, revision, and withdrawn patients, will be provided in the final study analyses.

22.4 Adverse Events

Time course distribution of Adverse Events for the safety population will be tabulated. Analysis of revision status will be done using a test of proportion such as Binomial test and Chi-square test unless otherwise noted. Additionally, the safety of R3 ODH-ODH will be assessed by analyzing the revision rate at 6 months, two years, 5 years, 7 years and 10 years post-operatively as well as by applicable operative and post-operative adverse events (device related or otherwise). Kaplan-Meier estimates will be used to analyze the survivorship of the prosthesis. For survivorship analyses, revision of one or more components will be defined as failure.

22.5 Site Selection

Investigators are selected by the Sponsor and selection is based on the training of the Investigator, the ability of his/her site to enroll an expected number of subjects in a reasonable period of time, the commitment to conduct the study according to the protocol, the ability to control investigational inventory, and other Sponsor stipulations and applicable regulatory requirements. The Investigators were selected because they have been instrumental in the design and development of the protocol from the early stages, and for their knowledge of the device. Investigators who have been sanctioned by regulatory agencies may not participate in the study.

23.0 Monitoring Procedures

23.1 Direct Access

This study will be monitored by the Sponsor or a qualified person designated by the Sponsor. This qualified person could be an employee of the Sponsor or of a contract research organization (Sponsor's agent). Documentation that the monitor has been trained will be maintained.

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

23.2 Pre-study

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

A site initiation visit will be performed by the Sponsor following the execution of the clinical agreement and documented IEC approval to provide training to the site on the specifics of the study and its conduct.

23.3 Interim Monitoring

The Sponsor or CRO will perform interim monitoring visits on a regular basis according to a schedule determined by the Sponsor. During these visits, the monitor will verify:

- the informed consent process occurred and is documented appropriately
- all inclusion/exclusion criteria were met
- source documentation is complete and available
- the data on CRFs is verified by the source documentation
- compliance with the protocol
- the reporting of adverse events occurred as required
- all required study documentation is complete and available

23.4 Closeout Visit

A study-close out visit will be performed by the Sponsor or CRO to retrieve and account for all remaining clinical data and investigational products. During study close-out, the monitor will review all Investigator files to ensure all required documents and records are on file, confirm the disposition of the investigational products and any other ancillary items used for the study, and review regulatory requirements regarding records retention and IEC reporting requirements. Any remaining investigational inventory will be collected and returned to the Sponsor at the end of the 10 year follow up if it was not collected following the enrollment period.

23.5 Documentation of Monitoring Visits

All activities associated with a monitor visit will be documented. This includes:

- Monitor visit log on site
- Monitor visit notification letter
- List of charts and/or hospital charts that were reviewed
- Review of the administrative binder
- Description of any site deficiencies
- Site compliance with protocol
- Description of any protocol deviations
- Assurance that informed consents were obtained and IEC review is current
- Device accountability
- Review of findings with available site personnel

All findings from the monitoring visit will be documented in a letter to the Investigator after the visit. Any site deficiencies will be noted and action items will be listed.

24.0 Risk Analysis

24.1 Risk and Precautions

Surgery Related Risks

The adverse events listed below can occur as the result of all THR surgery regardless of the specific device utilized:

- revision
- particulate wear debris generation
- device wear particle induced osteolysis, inflammation, etc.
- osteolysis or other bony abnormalities (including ectopic or heterotopic bone formation) as a result of wear, debris generation, or other causes
- loosening, bending, cracking, fretting, corrosion, stress shielding, dislocation, subluxation, improper loading, fracture of implant components, squeaking, clicking, stiffness, impingement, or mis-alignment
- worsened pain, function, range of motion, or change in limb length
- bone fracture
- 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
- pseudotumors
- trochanteric nonunion (when a transtrochanteric surgical approach is used)
- allergic reaction to materials in the implants
- large blood vessel damage and possible large blood loss (> 1500 ml) necessitating transfusion
- traumatic arthrosis from intraoperative positioning of the extremity
- delayed wound healing
- ipsilateral or contralateral limb problems due to length discrepancy, improper alignment, or muscle deficiency
- unsuccessful arthroplasty or failure to relieve symptoms.

Other adverse events are possible including death. These are events that may be reasonably expected to occur given a large enough subject population. A subject can experience almost any complication depending on the individual's circumstances. The frequency and severity will be a determining factor in assessing the importance of any specific event occurrence not listed.

In addition to general surgical risks, the risks listed below may occur as the result of treatment with the R3 ODH-on-ODH Hip System:

- Higher than normal wear of the ODH material may occur
- Allergic reaction to the material used in the implants
- Temporary or permanent device related noise such as clicking or squeaking
- Other unknown risks associated with the new material used in the device

24.2 Study Related Risks

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

- Radiologic Exposure
- Pain and bruising and possible infection at the site of blood draw
- Loss of confidentiality

24.3 Manner in Which Potential Risks will be Minimized

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

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 we will measure blood metal ion levels according to the assessment schedule.

Pseudotumor formation has been described in some cases of metal-on-metal prostheses. Risk of pseudotumor formation for this investigational device is unknown. Monitoring of pseudotumor formation will be conducted using study procedures for AE capture and through regular clinical monitoring of patient progress and radiologic imaging.

Some radiologic evaluations used in this study are not considered standard of care. Study-related radiologic exposure does not pose significant general health risk due to use of plain radiographs associated with low radiation levels. Pregnant women should not receive radiologic- assessments. Pregnancy and planned pregnancy is an exclusion criterion for the study. If a patient becomes pregnant during the course of this study, the patient will not participate in radiographic study assessments. Other study assessments and evaluations will continue according to the assessment schedule. The patient will resume radiographic assessments once pregnancy has ended. If the patient consents, the patient may be followed to obtain information about the pregnancy and outcome of the pregnancy.

Risk of pain and bruising and possible infection at the site of blood draw will be reduced by utilizing technicians that are trained in phlebotomy.

All Adverse Events will be reviewed on an ongoing basis by the Sponsor. Sponsor will review all adverse events to identify unanticipated device-associated adverse events.

The surgeon and manufacturer have proper experience, training, and device testing to support the use of the current device. The Investigators in this study have extensive

experience. The manufacturer is a large device company with a good track record of designing and producing quality orthopaedic products. Mechanical testing demonstrated the device will withstand in vivo requirements based on known factors. These efforts provide a superior risk minimization effect.

Adequate preclinical and mechanical testing and maintenance of quality manufacturing procedures (homogeneous composition, processing and design tolerances) combined with the history of prior use in other countries provides an excellent foundation on which to base the study of this type of device in a human clinical study. Careful attention to subject selection criteria and surgical implantation techniques may reduce the potential that components are exposed to forces that they were not intended and are aligned and seated properly. No guarantees can be made as to the success of this THA system.

24.4 Potential Benefits

Participation in this study may offer no direct benefit to subjects. However, most artificial joint replacement surgeries including THR surgery will allow a subject to have less pain, increased mobility, and the decreased use of medicines for pain especially early after surgery. The benefits of the study device should be compared with risks and benefits of other types of artificial joint replacement devices.

24.5 Justification for the Investigation

Investigation of the study device is justified because of its similarity to other commercially available arthroplasty devices, along with the possible benefits of reduced wear and particulate generation, in addition to reduced periprosthetic metal ion accumulation.

25.0 Investigator Responsibilities

The Investigator is responsible for ensuring that the investigation is conducted according to the Investigator Agreement, this Investigational Plan and applicable regulations as required. Investigator responsibilities are defined in ICH E6 GCP guidelines.

25.1 Investigator Records

The Investigator will maintain complete, accurate and current study records, including the following materials:

- Correspondence with the Sponsor, the Clinical Monitor, other Investigators, the IEC, or regulatory authorities
- Accountability of records or receipts:
- The use and disposition of all investigational devices and study materials
- The type and quantity of the device, the dates of its receipt, and the batch number or code mark;
- The names of all persons who received, used, or disposed of each device; and

- The number of devices that have been repaired, returned to the Sponsor, or otherwise disposed of, and the reason for such action;
- Study Subject Records including signed and dated informed consent forms, all source documentation, subject CRFs, queries and records of exposure of each subject to the device;
- All relevant observations, including records and reports concerning adverse effects (whether anticipated or unanticipated);
- Current study protocol and protocol deviation log, with dates and details of any reason for deviations from the protocol that could affect the scientific quality of the study or the rights, safety, or welfare of the subjects;
- The approved blank Informed Consent form and blank Subject CRFs;
- Certification that the Investigational Plan has been approved by all of the necessary approving authorities; and
- Signed Investigator Agreements with CV's of the Principal Investigator and any participating Co-Investigators attached updated at least annually.

25.2 Retention of Records

The Investigator must retain essential study documents until at least 2 years after the last marketing approval of the investigational product in an ICH region, or 15 years after the conduct of the study is complete, or for a longer period if required by the applicable local laws. The Investigator must obtain written permission from the Sponsor prior to destroying or moving study documents.

If an Investigator is unable to hold these records in his or her archives, the Investigator must make alternative arrangements. If an Investigator leaves the institution at which the study was conducted, another responsible party must be designated to maintain the records. Details of these arrangements must be documented in writing to the Sponsor.

25.3 Investigator Reports

The Investigator will be responsible for the following reports:

Adverse Event Reports: As described in this protocol.

Withdrawal of IEC Approval: The Investigator shall report to the Sponsor within 5 working days if, for any reason, the IEC withdraws approval to conduct the investigation. The report will include a complete description of the reason(s) for which approval was withdrawn.

Modification of the Protocol: Neither the Investigator nor Sponsor will modify this protocol without mutual agreement. After agreement to initiate the modification (in the form of a protocol amendment), the Investigator agrees not to institute this modification until instructed to do so by the Sponsor. It will be necessary to obtain IEC approval prior to implementation of any change in the protocol that may affect the scientific soundness or

the rights, safety, or welfare of the subjects involved. Notification shall be submitted to the IEC in no later than 5 working days.

Protocol Deviations: Protocol deviation is defined as any non-adherence to the protocol. Protocol deviations will be reported to Smith & Nephew. The Investigator must also report protocol deviations to the IEC as required by the IEC. Depending on the nature of the deviation, a decision will be made by the Investigator and Sponsor about whether the patient (for whom the departure from protocol was affected) is to continue in the study.

Implant of Device without Informed Consent: No Subject may be treated with the device without prior Informed Consent. Such treatment constitutes a violation of the study protocol. The Investigator shall submit a report indicating the circumstances for the occurrence to Smith & Nephew and to the reviewing IEC within five working days after the use occurs."

Progress Reports: The Investigator is required to submit six bi-monthly progress reports to the study Sponsor and to the reviewing IEC. Reports must include the number of subjects, a summary of all follow-up evaluations, and a general description of the study's progress.

Final Report: The Investigator will submit a final report to the Sponsor and to the IEC within 3 months of termination of the study, the termination of the Investigator's participation in the study, or at the completion of the study.

Other Reports: Upon request of the Sponsor or the IEC, the Investigator shall provide accurate, complete and current information.

25.4 Statement of Investigator

Prior to initiation of the study, all Investigators who will participate in the investigation must sign the Statement of Investigator. No Investigators will be added to the investigation until they have signed the agreement.

25.5 Financial Disclosure by Clinical Investigators

Each Investigator must disclose certain financial arrangements that may exist between the Investigator and Smith & Nephew. This information will be collected and maintained confidentially at Smith & Nephew and will be available for review upon request. This information must be updated promptly by the Investigator and submitted to the Sponsor if any changes occur through the duration of the study and for one year following the completion of the study.

26.0 Insurance

Public/Products liability insurance has been purchased by Smith & Nephew worldwide and incorporates coverage for personal injury in respect of clinical studies.

27.0 Other

Before the start of the study the Principal Investigator will take responsibility for informing the National Health Research Ethics Council, the South African National Clinical Trials register (SANCTR) and/or regulatory authority (if applicable) of research to take place.

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21 CFR 812