A Prospective, Multi-center, Randomized, Controlled Study to Evaluate the Safety and Efficacy of the OR3O™ Dual Mobility System versus conventional single bearing design Total Hip System in Primary Total Hip Arthroplasty (THA) Procedures

Protocol No：	OR3O.2019.10 (China)
Protocol Version and Date:	1.0, 18AUG2020
Investigational Product(s):	OR3O™ - Dual Mobility System
Management Type of Investigational Product：	Category III Medical Device Requiring Clinical Trial Approval Yes☐ No☒
Similar Products in China:	Yes☒ No☐
Leading Site of Clinical Trial:	The First Affiliated Hospital of Xinjiang Medical University
Site of Clinical Trial:	Peking University Third Hospital The Ninth People's Hospital affiliated to Shanghai Jiao Tong University Medical College The Third Hospital of Hebei Medical University
Sponsor:	Smith & Nephew Medical (Shanghai) Limited

Sponsor Name and Address: SMITH & NEPHEW MEDICAL (SHANGHAI) LIMITED.
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1. SIGNATURES

1.1 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

This page will be returned to Smith & Nephew Medical (Shanghai) Limited and a copy retained at the investigational site.

I have read the attached protocol entitled "A Prospective, Multi-center, Randomized, Controlled Study to Evaluate the Safety and Efficacy of the OR3O™ Dual Mobility System versus conventional single bearing design Total Hip System in Primary Total Hip Arthroplasty (THA) Procedures", version <1.0>, dated <18/AUG/2020>, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in 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 Medical (Shanghai) Limited.

Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.2 COORDINATING INVESTIGATOR APPROVAL

I have read the attached protocol entitled "A Prospective, Multi-center, Randomized, Controlled Study to Evaluate the Safety and Efficacy of the OR3O™ Dual Mobility System versus conventional single bearing design Total Hip System in Primary Total Hip Arthroplasty (THA) Procedures", version <1.0>, dated <18/AUG/2020>, and agree to abide by all provisions set forth herein.

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Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.3 INVESTIGATOR APPROVAL

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Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.4 INVESTIGATOR APPROVAL

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I agree to comply with the Investigator's Obligations stipulated in 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 Medical (Shanghai) Limited.

Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.5 SPONSOR APPROVAL

	Name and Title	Signature and Date / DocuSign Stamp
Head of China Clinical Affairs	Julian Yang, Director, China Clinical Affairs	DocuSigned by: Yang, Julian Signer Name: Yang, Julian Signing Reason: I approve this document Signing Time: 31-Aug-2020 | 02:52:01 BST 7874D1D26E584792AFFC91EBB7CEF6D0
Head of Global Clinical Strategy	Yancy Shaherah Senior Director, Global Clinical Strategy	DocuSigned by: Yancy, Shaherah Signer Name: Yancy, Shaherah Signing Reason: I approve this document Signing Time: 31-Aug-2020 | 14:11:18 BST E36A63EADAD542EE983507B2AC8E7B41
Head of Global Biostatistics	Alan Rossington, Director Biostatistics and Data Management	DocuSigned by: Alan, Rossington Signer Name: Alan, Rossington Signing Reason: I approve this document Signing Time: 28-Aug-2020 | 13:53:44 BST 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Medical Affairs Representative	Orlandini Luca，Vice President Medical Affairs Global Clinical Affairs	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 26-Aug-2020 | 20:09:15 BST FC872951AC1C4261B85EC7A7CD09ACDC
Regulatory Representative	Kerry Geng, Senior Director, Head of Regulatory Affairs and Quality, Greater China	DocuSigned by: Kerry Geng Signer Name: Kerry Geng Signing Reason: I approve this document Signing Time: 26-Aug-2020 | 07:30:17 BST 915D993DECAC45C6B47B47118A847FBA

2. SYNOPSIS

Title of Study:	A Prospective, Multi-center, Randomized, Controlled Study to Evaluate the Safety and Efficacy of the OR3O™ Dual Mobility System versus conventional single bearing design Total Hip System in Primary Total Hip Arthroplasty (THA) Procedures
Study Design:	A prospective, multi-center, randomized, controlled, 2-arm study with follow up to 2 years.
Study Type:	Pre-market study
Study Product:	OR3O™ Dual Mobility System is comprised of a diffusion-hardened, oxidized zirconium acetabular liner (OR3O™ Liner), and an insert of highly cross-linked polyethylene (OR3O™ XLPE Insert). In this study, the OR3O™ Dual Mobility System will be used in combination with R3™ Acetabular Shell and a Smith & Nephew Oxinium (Ox) femoral head.
Comparison Group:	A conventional, single-bearing design Total Hip System comprised of R3™ Acetabular Shell with XLPE liner and a Smith & Nephew Oxinium (Ox) femoral head.
Study Purpose:	The purpose of this study is to compare OR3O™ Dual Mobility System to a conventional, single-bearing design Total Hip System in subjects who undergo Primary THA. Data collected in this study will be used to support NMPA regulatory approval of OR3O™ Dual Mobility System in China as well as to support and maintain product registration in global markets.
Primary Objective:	Assess safety and efficacy of the OR3O™ Dual Mobility System in Primary THA at 1 year postoperative.
Secondary Objective(s):	Assess safety and efficacy of the OR3O™ Dual Mobility System and compatible components in Primary THA up to 2 years after surgery.
Other Objective(s):	Assess the hip dislocation and hospital readmission up to 2 years after device implantation.

Sample Size:	Sample size calculation is based on the assumption that in order to be considered of comparable efficacy, Study Arm (dual mobility cohort) must obtain at least 90% of the efficacy in the Controlled Arm (conventional cohort). It is expected and further assumed that 95% of the Harris Hip Score at 12 months postoperative will have a rating of good or excellent (80-89, ⩾ 90), then 76 evaluable subjects per group would be required to carry out the hypothesis testing at 12 months postoperatively. Assuming an attrition rate of 10% at 1 year, 85 subjects per arm, in total of 170 subjects are needed.
Number of Study Sites:	4 study sites in China

Inclusion Criteria:	• Subject is a suitable candidate for implanting the OR3O™ Dual Mobility System or single-bearing design Total Hip System in primary total hip replacement in the Investigator's judgement.
	• Subject is skeletally mature in the Investigator's judgement.
	• Subject is 18 – 80 years old (inclusive).
	• Subject is receiving total hip replacement for the first time on the affected hip.
	• Subject has any of the following conditions:
	  ○ Advanced degeneration of the hip joint as a result of degenerative, post-traumatic, or rheumatoid arthritis(RA);
	  ○ Fracture or avascular necrosis of the femoral head;
	  ○ All forms of osteoarthritis(OA);
	  ○ Patients with hips at risk of dislocation;
	  ○ Femoral neck fracture or proximal hip joint fracture.
	• Subject provides written informed consent for study participation using an Ethical Committee (EC) approved consent form before any study procedures are performed, including pre-operative data review and/or collection of data on electronic Case Report Forms (eCRFs).

	• Subject is willing and able to participate in required follow-up visits and is able to complete study activities. • Subjects with preoperative HHS ⩽ 79 (fair or worse category).
Exclusion Criteria:	• Subject has conditions that would eliminate or tend to eliminate adequate implant support or prevent the use of an appropriately-sized implant, e.g.: o blood supply limitations; o insufficient quantity or quality of bone support, e.g., osteoporosis, metabolic disorders which may impair bone formation, radioactive bone disease, tumor around hip joint, and osteomalacia; o infections or other conditions which may lead to increased bone resorption. • Subject has dysplasia of hip joint with CROWE Grade III, IV. • Subject has weak constitution or failing to endure the surgery due to other diseases of the body. • Subject has bodily disease(s) that may interfere with THA survival or outcome. • Subject has life expectancy of less than 2 years. • Subject has mental or neurological conditions which impair the subject's ability or willingness to restrict activities that may put the affected limb at risk. • Subject has physical conditions or activities which tend to place extreme loads on implants, e.g., Charcot joints, muscle deficiencies, multiple joint disabilities. • Subject has neuromuscular dysfunctions (paralysis, myolysis and abductor muscle weakness) which will cause unstable hip joint or abnormal gait after surgery. • Subject has a mental 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 has an active infection – systemic or at the site of intended surgery. • Subject has a Body Mass Index ⩾ 40.0 kg/m² • Subject has a known allergy to any component of the devices used in the study. • Subject is pregnant or breast feeding. • Subject is entered in another investigational drug, biologic, or device study within 30 days of active study participation. • Subjects that are expected with poor compliance. • Subjects with complications of other diseases are limited to participate in the research, not able to comply with the follow-up or have impact on scientific integrity. • Subjects with preoperative HHS ⩾ 80 (good to excellent category). • Subject has other diseases or conditions that investigator considers not appropriate to participate in the study.
Study Duration:	Approximately. 36 months (3 years) Enrollment period: approximately. 12 months Follow-up period: 24 months
Primary endpoint:	Proportion of excellent (⩾ 90) or good (80-89) HHS scores at 12 month postoperative.
Secondary endpoint(s):	Safety and efficacy evaluated in this study at baseline, 6 weeks, 3 months, 6 months, 1 year and 2 years after surgery as measured by: • Survivorship of the OR3O™ Dual Mobility System (no revision due to any reason) • Survivorship of controlled system • Harris Hip Score (HHS)

	• EuroQol(European Quality of Life) five-dimensional Five-level (EQ-5D-5L) score
	• Hip Disability and Osteoarthritis Outcome Score for Joint Replacement (HOOS JR.)
	• Radiographic Assessment
	  ○ Implant position/Orientation
	  ○ Implant subsidence/migration
	  ○ Periprosthetic fractures
	  ○ Heterotopic ossification
	  ○ Radiolucencies
	  ○ Osteolysis
	  ○ Implant loosening
	  ○ Stress Shielding

Other exploratory endpoint(s):	• Dislocation percentage of the hip up to 2 years after device implantation. • Hospital readmission percentage (cumulative) by 30, 60, 90 days of discharge due to any reason related to study device or study procedure.
Safety Data:	• All adverse events (AEs) occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events. • Device Deficiencies (DDs)

STUDY SCHEDULE

Schedule of events	Pre-Op Data	Operative / Discharge	6 Weeks (42 – 7/+14 days)	3 months (90 ±30 days)	6 months (180 ±30 days)	1 yr. (365 ±60 days)	2 yr. (730 ±60 days)
Informed Consent	x						
Inclusion/ Exclusion	x						
Demographics	x						
Medical History	x						
Vital Signs	x						
Preoperative Lab Examinations (eg. Blood Routine Examination Biochemical Examination, Coagulation Examination) [1]	x						
Pregnancy Test[2]	x						
Operative Data		x					
Discharge Data		x					
Implant status			x		x	x	x
HHS	x		x	x	x	x	x
EQ-5D-5L	x		x	x	x	x	x
HOOS JR.	x		x	x	x	x	x
Radiographic Assessment	(x)[3]	(x)[4]	(x)[4]	x	x	x	x
Concomitant Medications[5]		x	x	x	x	x	x
Safety Assessment (AEs, DDs)		x	x	x	x	x	x
End of Study/ Exit		x	x	x	x	x	x

1 If applicable, where, for preoperative lab examinations, only those within Day 0~14 before the operation are acceptable.

The Preoperative Lab Examinations required to be performed include:

- Blood routine examination: Haemoglobin, Platelet count, White Blood Cell count, neutrophil count, erythrocyte sedimentation rate
- Coagulation examination: Prothrombin time, activated partial thromboplastin time), thrombin time, D-dimer
- Biochemical examination: Urea or urea nitrogen, creatinine, AST, ALT, blood glucose
- Other examination: Erythrocyte sedimentation rate

2 If applicable, where, the pregnancy test is only suitable for females of child-bearing potential, neither premenstrual females nor sterilized or postmenopausal (i.e., 12-month amenorrhea without alternative medical reasons) females.

3 If X-ray image has been done within 30 days before the Informed Consent Form is signed, and the data is available, they can be used as the data for screening before operation.

4 Radiographic assessment performed at discharge or 6 weeks follow-up visit only.

[5] All combination medications associated with AEs or serious adverse events (SAEs) are reported.

3. CONTENTS

3.1 TABLE OF CONTENTS

3.2 List of Tables

3.3 List of Figures

3.4 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADE	Adverse Device Effect(s)
ADL	Activities of Daily Living
AE	Adverse Event(s)
ANCOVA	Analysis of Covariance
AP	Anteroposterior
ASADE	Anticipated serious adverse device effect
AVN	Avascular Necrosis
BMI	Body Mass Index
BSI	British Standards Institute
CE	ConformitéEuropéne
CI	Confidence Interval
CoCr	Cobalt Chrome
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CV	Curriculum Vitae
DD	Device Deficiency(ies)
DH	Diffusion Hardened
EC	Ethics Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol (European Quality of Life) five-dimensional Five-level
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Definition
HA	Hydroxyapatite
HHS	Harris Hip Score
HIPAA	Health Information Portability Accountability Act
HSA	Health Science Authority
HOOS JR.	Hip disability and Osteoarthritis Outcome Score for Joint Replacement
HRQOL	Health Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	Instructions for Use
IP	Investigational Product
IPD	Intra-prosthetic Dislocation
ISF	Investigator Site File
ITT	Intent-to-Treat
KM	Kaplan-Meier
LL	Lower Limit
LOCF	Last Observation Carry Forward
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
NDA	Non-Disclosure Agreement
NMPA	National Medical Products Administration
OA	Osteoarthritis
Ox	Oxinium
PI	Principal Investigator

Abbreviation	Definition
PP	Per-protocol Population
QA	Quality Assurance
QC	Quality Control
RA	Rheumatoid Arthritis
S+N	Smith & Nephew
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration
THA	Total Hip Arthroplasty
UL	Upper Limit
USADE	Unanticipated Serious Adverse Device Effect(s)

4. INTRODUCTION

4.1 BACKGROUND

Arthritis is a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. Two common etiologies of arthritis are degeneration of the joint, osteoarthritis (OA), and inappropriate inflammatory response, rheumatoid arthritis (RA). OA is characterized by loss of cartilage, remodeling of adjacent bone, and inflammation in the affected joint (2, 9). RA is a progressive inflammatory disease that eventually causes systemic joint damage and disability (1).

Avascular necrosis (AVN) has several etiologies but fundamentally results from a decrease in blood flow to the femoral head, leading to cellular death (4, 11).

For patients with any of these indications who have exhausted available conservative interventions or advanced degeneration of the joint, joint replacement is considered the most effective treatment.

Total hip arthroplasty (THA) is an extremely successful intervention that significantly reduces pain, increases mobility, and restores function in patients with degenerative joint disease (7). It is most frequently employed to treat symptomatic end-stage OA (7, 12). Other indications include RA, AVN, femoral neck fracture, and developmental dysplasia of the hip. Hip arthroplasty device designs consist of a femoral component, acetabular component, and bearing surface (7). The materials used and fixation methods vary, allowing the surgeon to choose the most effective system for each case (20). Current research in THA focuses on optimizing clinical outcomes, reducing complications, and improving implant designs by researching materials and novel design advancements to mimic normal physiology (10).

Dual-mobility hip systems incorporate two distinct articulations. These two articulations allow for greater range of motion, a greater head-to-neck ratio, and a more physiologic effective head size that increases the jump distance and hence resistance to dislocation (13, 19).

The primary articulation is between the femoral head and the polyethylene insert, and the second at the interface between the convex surface of the polyethylene insert and the acetabular liner.

The primary articulation is engaged during the majority of activities with normal range-of-motion requirements. The secondary articulation is engaged during activities that exceed normal range of motion.

The OR3O™ Dual Mobility System provides modular dual mobility using an advanced bearing surface, OXINIUM DH (Diffusion Hardened) and a highly cross-linked polyethylene (XLPE). Dual mobility components are used with compatible Smith & Nephew (S+N) acetabular shells and femoral heads.

This study is a pre-market study of imported OR3O™ Dual Mobility System as an investigational device. Refer to the Investigator's Brochure for comprehensive literature review, preclinical and clinical safety data, and risk analysis.

4.2 LITERATURE SUMMARY

Dual mobility acetabular components have been shown to provide increased stability after THA (6, 22). A growing body of literature reports reduced dislocation rate in primary and revision arthroplasty using dual-mobility (3, 5, 6, 18). The main complication associated with dual-mobility is intra-prosthetic dislocation (IPD), which is characterized by the loss of the positive locking between the femoral head and the polyethylene insert; although the mechanism is not yet completely understood (6, 8). A systematic review of 17,908 THAs using dual mobility acetabular components reported that the rate of dislocation was 0.9% in primary THA and 3.0% in the revision THA group. The mean rate of IPD was 0.7% in primary and 1.3% in revision THAs (6).

Wear and loosening are commonly reported complications for dual mobility systems and are accentuated due to larger diameter articulations with multiple surfaces (14).

A higher rate of instability is also reported with displaced femoral neck fractures, creating increased utilization of dual mobility THA for these patients. A retrospective study compared the results of 171 bipolar hemiarthroplasty and 175 THA performed using dual mobility in patients with displaced femoral neck fractures. The rate of dislocation in the THA group was significantly lower than the bipolar hemiarthroplasty group (14.6% versus 4.6%) (16, 21). Another prospective multicenter study reported a short-term dislocation rate of 1.4% when THA with dual mobility was used in femoral neck fracture patients (16, 21).

Utilization of dual mobility components have also shown promising results in other high risk dislocation populations such as obese patients and patients with neurological disorders (16). Dual mobility has also been found beneficial for young and active patients, particularly as implants have improved, causing wear-related complications to reduce. One study, with a 22 year follow-up, reported the dual mobility cup survival rate of 77% in patients under 50 years of age (mean age: 41 years) (16).

4.3 STUDY PURPOSE

The purpose of this study is to compare OR3O™ Dual Mobility System to a conventional, single-bearing design Total Hip System in subjects who undergo Primary THA to assess the safety and efficacy of the OR3O™ Dual Mobility System. Data collected in this study will be used to support NMPA regulatory approval of OR3O™ Dual Mobility System in China as well as to support and maintain product registration in global markets.

4.4 SAFETY CONSIDERATIONS

4.4.1 Intended Use

The OR3O™ Dual Mobility System is intended for use in Primary and Revision THA in skeletally mature subjects.

4.4.2 Indications

- Advanced degeneration of the hip joint as a result of degenerative, post-traumatic, or rheumatoid arthritis.
- Fracture or avascular necrosis of the femoral head.
- Failure of previous hip surgery: joint reconstruction, internal fixation, arthrodesis, hemiarthroplasty, surface replacement arthroplasty, or total hip replacement.
- All forms of osteoarthritis.
- Patients with hips at risk of dislocation.
- Femoral neck fracture or proximal hip joint fracture.

The OR3O™ Dual Mobility System is intended for single use only. The modular OR3O Dual Mobility Liners and Inserts are to be implanted without bone cement.

Mating components may be indicated for use without bone cement.

4.4.3 Contraindications

- Do not use OR3O™ Liners with any polyethylene dual mobility insert other than Smith & Nephew OR3O™ XLPE Inserts of matching bearing size.
- Do not use OR3O™ Liners with metal or ceramic femoral heads made from materials such as stainless steel, CoCr, alumina, zirconia toughened alumina, OXINIUM, or OXINIUM DH.
- Conditions that would eliminate or tend to eliminate adequate implant support or prevent the use of an appropriately-sized implant, e.g.:
    - blood supply limitations;
    - insufficient quantity or quality of bone support, e.g., osteoporosis, or metabolic disorders which may impair bone formation, and osteomalacia; and
    - infections or other conditions which may lead to increased bone resorption.
- Mental or neurological conditions which may tend to impair the patient's ability or willingness to restrict activities putting the affected limb at risk.
- Physical conditions or activities which tend to place extreme loads on implants, e.g., Charcot joints, muscle deficiencies, multiple joint disabilities, etc.
- Skeletal immaturity.
- Skirted femoral heads are contraindicated for use with this device.

5. OBJECTIVE(S)

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess safety and efficacy of the OR3O™ Dual Mobility System in Primary THA at 1 year postoperative.

5.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to assess safety and efficacy of the OR3O™ Dual Mobility System and compatible components in Primary THA up to 2 years after surgery.

5.3 OTHER OBJECTIVES

Other objectives of the study are to assess the hip dislocation percentage and hospital readmission percentage (cumulative) up to 2 years after device implantation.

6. INVESTIGATIONAL PRODUCTS

6.1 IDENTIFICATION

6.1.1 Investigational Product

The OR3O™ Dual Mobility System (liner and insert) is an acetabular system for THA. It is intended for use in Primary and Revision THA in skeletally mature patients.

OR3O™ Dual Mobility System is comprised of a diffusion-hardened, oxidized zirconium (Oxinium™) acetabular liner with a highly polished inner surface of zirconia, a machined locking taper and backside of Zr-2.5Nb alloy, and an insert of highly cross-linked polyethylene (XLPE).

The OR3O™ Liner is assembled into an acetabular shell with a locking taper. The outer diameter of the OR3O™ XLPE Insert articulates within the OR3O™ Liner and features an inner articular surface, which engages with oxidized zirconium (Oxinium™) or CoCr alloy femoral heads of sizes 22mm (for shell sizes 48mm-52mm) and 28mm (for shell sizes 54mm-74mm). Femoral heads are retained within the OR3O™ XLPE Insert by means of a snap fit locking mechanism.

The OR3O™ Dual Mobility System (liner / insert) is combined with existing commercially available S+N acetabular shells and femoral heads, which will be referred to as OR3O™ Dual Mobility Construct within this protocol. The OR3O™ Liner is designed to mate with a dedicated R3™ or REDAPT™ Modular Press-fit acetabular shell with outer diameter sizes of 48mm to 74mm.

Figure 6-1 illustrates the OR3O™ Dual Mobility Construct with an acetabular shell (with optional screws), an Oxinium™ DH Liner, a XLPE Insert and a femoral head.

Figure 6-1: OR3O™ Dual Mobility Construct

In this study, non-Hydroxyapatite (HA) R3™ Acetabular Shells and Oxinium femoral head will be used in sites in China. The use of screws to secure the acetabular shell is at the discretion of the surgeon.

The OR3O™ Dual Mobility System will be combined with a compatible Smith & Nephew femoral stem.

6.1.2 Comparator Treatment

The comparator treatment in the study is a conventional, single-bearing design Total Hip System comprised of R3™ Acetabular Shell with XLPE liner and a Smith & Nephew Oxinium (Ox) femoral head.

6.2 PRODUCT USE

Each device is packaged with an IFU (Document ID 81104400) to ensure that the device is used properly and for the intended purposes. It is the Investigator's responsibility to ensure adherence to this IFU as well as Investigator's Brochure.

6.3 PACKAGING AND LABELING

Packaging and labeling will be prepared to meet China current laws and regulatory requirements. Package integrity and labelling should be verified prior to use of the product.

6.3.1 Labeling of Investigational Product

In China, commercially available products (acetabular shells and femoral heads) are combined with an investigational product (OR3O™ Dual Mobility System) to form the OR3O™ Dual Mobility Construct. The R3™ Acetabular Shells and Oxinium femoral head to be used in this study are commercial products in China and will be labeled and packed as per the standard commercial packaging.

OR3O™ Dual Mobility liner and insert are investigational products in China. The standard commercial packaging as marketed in the US will be used for these investigational products. Additional labels will be included on the commercial packaging to specify that the product is for investigational use only in order to meet regulatory requirements for use of investigational devices in China.

6.3.2 Comparator Product

The comparator product to be used in this study are commercial products in China and will be labeled and packed as per the standard commercial packaging.

6.4 PRODUCT ACCOUNTABILITY PROCEDURES

No product accountability procedures will be applied for the acetabular shells, femoral heads and femoral stems in all study sites as these are commercially available products in China.

The study includes the use of investigational devices in China and the following product accountability procedures will be applied for OR3O™ Dual Mobility liners and inserts:

The investigational site will maintain an inventory of the investigational product (IP). The Sponsor or its designee will provide a log(s) to facilitate IP inventory control. The log will contain details of receipt, use, returns etc. of IP. All IP accountability logs must be retained in the Investigator Site File (ISF). These records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time. IP Management Instructions will be provided by the Sponsor to the site detailing all additional forms that might need completion (e.g. confirmation of receipt) for IP control.

The Study Monitor will ensure that the procedures and records are in place for the appropriate reconciliation of all IP. As part of monitoring, the Study Monitor will check that site personnel are following the proper procedures for accountability and completing all necessary documentation.

6.5 SURGICAL TECHNIQUE

All study related procedures with the OR3O™ Dual Mobility System must be performed according to the approved surgical technique.

Surgical techniques are available for different OR3O™ Dual Mobility System / acetabular shell combinations. The appropriate surgical technique needs to be followed when using the OR3O™ Dual Mobility System in combination with R3™ Acetabular Shells (Document ID 71381776).

Surgeons selected to participate in this study will be familiar with implanting Dual Mobility Systems and have expertise in the study procedure.

If device replacement/reconditioning is required during the primary surgery, the investigator shall perform device replacement/reconditioning on the subject in accordance with conventional medical device replacement/reconditioning.

7. SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 SUBJECT POPULATION

A total of 170 hips will be enrolled into the study at 4 study sites in China.

Subjects may be enrolled and randomized in the study with one hip implanted with either the OR3O™ Dual Mobility System in combination with R3™ Acetabular Shells and a Smith & Nephew Oxinium femoral head or the single-bearing design Total Hip System comprised of R3™ Acetabular Shell with XLPE liner and a Smith & Nephew Oxinium femoral head. Therefore, enrollment refers to the number of subjects.

7.2 INCLUSION CRITERIA

Subjects will be considered qualified for enrollment if they meet the following criteria:

1. Subject is a suitable candidate for implanting the OR3O™ Dual Mobility System in primary total hip replacement in the Investigator's judgement.
2. Subject is skeletally mature in the Investigator's judgement.
3. Subject is 18 – 80 years old (inclusive).
4. Subject is receiving total hip replacement for the first time on the affected hip.
5. Subject has any of the following conditions:
   - Advanced degeneration of the hip joint as a result of degenerative, post-traumatic, or rheumatoid arthritis(RA);
   - Fracture or avascular necrosis of the femoral head;
   - All forms of osteoarthritis(OA);
   - Patients with hips at risk of dislocation;
   - Femoral neck fracture or proximal hip joint fracture.
6. Subject provides written informed consent for study participation using an Ethical Committee (EC) approved consent form before any study procedures are performed, including pre-operative data review and/or collection of data on Case Report Forms.
7. Subject is willing and able to participate in required follow-up visits and is able to complete study activities.
8. Subjects with preoperative HHS $\leqslant$ 79 (fair or worse category).

7.3 EXCLUSION CRITERIA

Any one (1) of the following criteria will disqualify a potential subject from participation in the study:

1. Subject has conditions that would eliminate or tend to eliminate adequate implant support or prevent the use of an appropriately-sized implant, e.g.:
   - blood supply limitations;
   - insufficient quantity or quality of bone support, e.g., osteoporosis, metabolic disorders which may impair bone formation, radioactive bone disease, tumor around hip joint, and osteomalacia;
   - infections or other conditions which may lead to increased bone resorption.
2. Subject has dysplasia of hip joint with CROWE Grade III, IV.
3. Subject has weak constitution or failing to endure the surgery due to other diseases of the body.
4. Subject has bodily disease(s) that may interfere with THA survival or outcome
5. Subject has life expectancy of less than 2 years.
6. Subject has mental or neurological conditions which impair the subject's ability or willingness to restrict activities that may put the affected limb at risk.
7. Subject has physical conditions or activities which tend to place extreme loads on implants, e.g., Charcot joints, muscle deficiencies, multiple joint disabilities.
8. Subject has neuromuscular dysfunctions (paralysis, myolysis and abductor muscle weakness) which will cause unstable hip joint or abnormal gait after surgery.
9. Subject has a mental 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.
10. Subject has an active infection – systemic or at the site of intended surgery.
11. Subject has a Body Mass Index ≥ 40.0 kg/m^2
12. Subject has a known allergy to any component of the devices used in the study.
13. Subject is pregnant or breast feeding.
14. Subject is entered in another investigational drug, biologic, or device study within 30 days of active study participation.

15.	Subjects that are expected with poor compliance.
16.	Subjects with complications of other diseases are limited to participate in the research, not able to comply with the follow-up or have impact on scientific integrity.
17.	Subjects with preoperative HHS ≥ 80 (good to excellent category).
18.	Subject has other diseases or conditions that investigator considers not appropriate to participate in the study.

7.4 SCREENING

Investigators should consecutively screen all subjects undergo primary THA to determine whether they meet all inclusion and none of the exclusion criteria. Participating study sites are required to document all screened subjects considered for inclusion in this study on a Screening and Enrollment Log. If a subject is excluded from the study, the reasons for exclusion will be noted on the Screening and Enrollment Log.

7.5 INFORMED CONSENT

Investigators are responsible for obtaining and documenting the voluntary informed consent of the study subjects before conducting any study procedures or examinations, per International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

Prior to beginning the study, in obtaining the informed consent, the purpose and nature of the study should be explained to the subject in their native language. The subject, will then **read**, **sign**, and **personally date** the EC approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, and the original appropriately filed at the investigative site.

The informed consent process must be fully documented in the subject's medical record.

If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and personally date the Informed Consent Form (ICF). Where this is not possible, due

to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given.

The informed consent form and any other written information provided to subjects shall 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 EC approval in advance of use.

7.6 ENROLLMENT

The site initiation shall be started only after the EC has approved and the clinical trial agreement has signed at each site. Subjects for whom the consent process has been completed and have been implanted with the study product are considered enrolled. Competitive enrollment continues until the completion of enrolled 170 subjects.

If the subject does not have the OR3O™ Dual Mobility System or controlled system implanted after signing an informed consent form, the subject will be considered to be a Screen Failure. Screen Failures will not count into the total number of enrolled subjects.

7.7 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for 2 consecutive visits, and study personnel are unable to contact the subject.

Some actively enrolled subjects will not return for follow-up exams on time. Study personnel must make a reasonable effort to contact the subject and document the following contact attempts before declaring a subject to be lost to follow-up: the subject has been contacted according to the site's policies, but no fewer than two documented phone contacts (at least one of these attempted phone contacts conducted by the Investigator) and one written attempt without response. The written attempt can either be a certified letter or an email with read confirmation dependent on accepted ways of communication within the study regions. Copies of all attempts to reach the subjects by 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 subject's source documents.

7.8 WITHDRAWAL

7.8.1 Withdrawal from Treatment

Subjects may be withdrawn from having the study device implanted at a date close to surgery or during surgery for the following reasons:

- At the discretion of the Investigator due to:
  - A change in treatment being clinically warranted.
  - An adverse event.
  - Any other significant reason identified by the Investigator.

Subjects who provide informed consent but do not receive the study device for any reason will be considered a Screen Failure. Screen Failures will not count into the total number of enrolled subjects.

If at any point during the study, the study device needs to be revised for any reason the following will apply: Intraoperative data from the revision surgery will be collected including implant information used for revision THA. Subjects will terminate the study following revision surgery. Subjects shall be followed by the Investigator according to sites' standard of care in order to monitor the subject's health status and the outcome of the revision. Data collected following the revision surgery will be reported as follow-up data to the adverse event. Data will not be included as study data but presented separately as safety data. Data collected upon the point of revision will be included as study data.

7.8.2 Withdrawal from Study

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

- Subject noncompliance (e.g., did not follow instructions for regular follow up);
- Subject lost to follow-up;
- The Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study;
- Concurrent illness;

- Adverse Events/Adverse Device Effects
- Any other significant reason identified by the Investigator.

For each case, information will be recorded in the source document and the electronic Case Report Form (eCRF) detailing circumstances leading to the withdrawal. Data collected upon point of withdrawal will be included as study data.

Subjects who drop out or are withdrawn will not be re-entered into the study at a later date. If at any point during the study, the total hip prosthesis needs to be revised for any reason the following will apply: Subjects shall continue to have follow-up visits in order to monitor the subject's health status. Potential data following the revision surgery will not be included as study data but presented separately as safety data.

7.8.3 Subject's Withdrawal of Consent to Participate in Study

Study participation is voluntary, and subjects may withdraw at any point during the study without giving their reason for doing so. Where subjects withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's privacy. The reason for withdrawal will be recorded in the eCRF and source documents.

If withdrawal is after OR3O™ Dual Mobility System or controlled system implantation, then the Investigator should inform the subject of any recommended follow-up visits to monitor subject safety.

7.8.4 Use of Data Following Withdrawal

In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected after withdrawal of consent.

8. STUDY DESIGN

8.1 STUDY DESIGN AND JUSTIFICATION

This study is a prospective, multi-center, randomized, controlled, 2-arm study to assess safety and efficacy of the OR3O™ Dual Mobility System in Primary THA. Subjects meet the inclusion/exclusion criteria specified in the protocol will be randomized to receive implantation

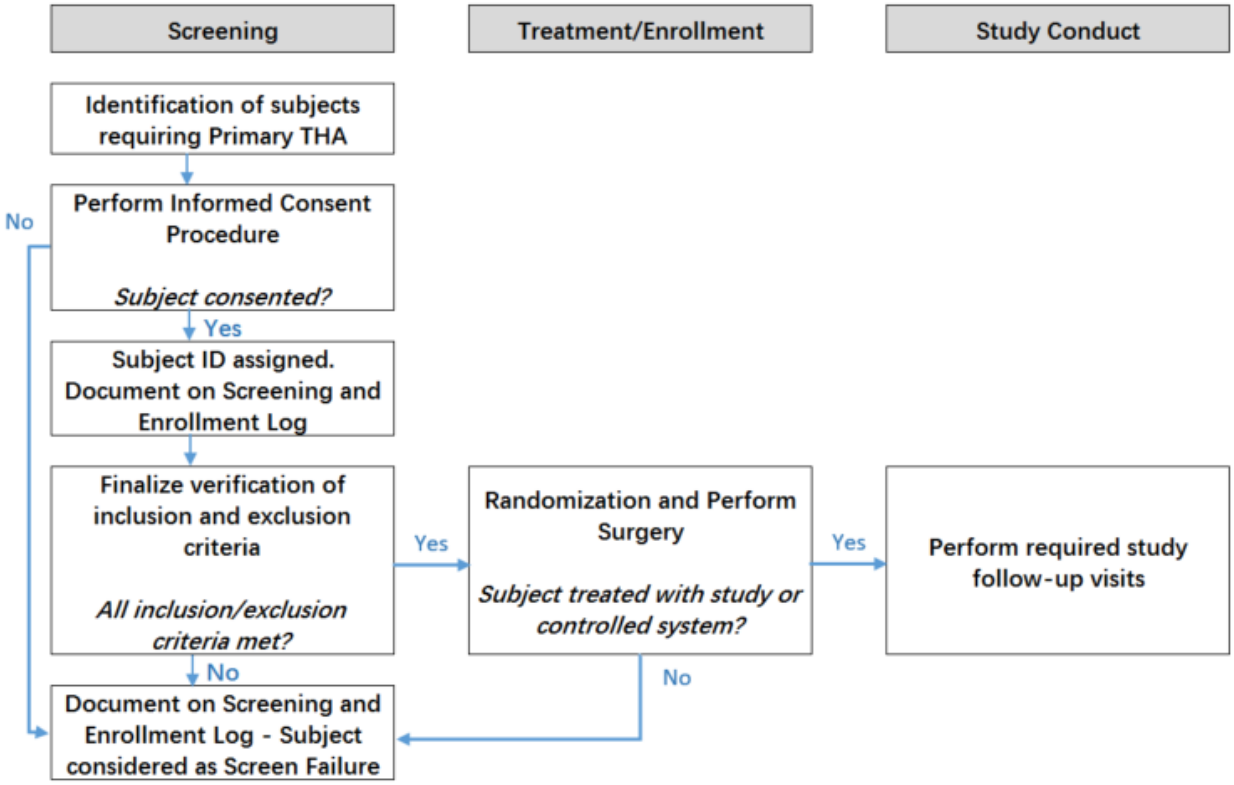
with the investigational product or controlled system. Up to 4 sites in China will participate competitive enrolling a total of 170 hips, whereas the number of subjects enroll in each study site should be no more than 85 cases.

The study is expected to enroll all subjects within a 12 months' timeframe. Subjects will be followed-up at 6 weeks, 3, 6, 12 and 24 months after surgery.

In this study, a summary of 1 year follow-up data will be reported to NMPA for regulatory approval and a 2 year follow-up will be sufficient to identify and assess the risk of any associated unacceptable adverse event over this time period. The study duration will be sufficient to allow conclusions about likely safety and efficacy of the OR3O Dual Mobility System in a longer term.

Figure 8-1 details the different steps of study conduct from screening to enrollment and follow-up.

Figure 8-1: Study Flowchart



Subjects may be assigned a subject ID, but then not enrolled in the study (e.g. did not receive the study or controlled device or decided not to participate in the study).

8.2 ALLOCATION AND BLINDING

8.2.1 Treatment Allocation

This study is randomized. All subjects who sign the ICF and meet inclusion / exclusion criteria will randomly receive either the OR3O™ Dual Mobility System in combination with R3™ and a Smith & Nephew Oxinium femoral head, or a conventional, single-bearing design Total Hip System comprised of R3™ Acetabular Shell with XLPE liner and a Smith & Nephew Oxinium femoral head at 1:1.

8.2.2 Blinding

To minimize the impact of bias associated with treatment assignment during the study, since the surgeon cannot be blinded to the identity of the surgical product, it is planned to appoint an independent evaluator in each study site, who will be blinded and responsible for completing study related scoring at each follow-up.

8.3 DATA MANAGEMENT

8.3.1 Source Document

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject (source documents). Source data is all information and original records of clinical findings, observations, or other activities necessary for the evaluation of the study. These original documents and data records include but are not limited to inpatient or outpatient medical records, clinical and office charts, laboratory notes, memoranda, subjects' memory aids or evaluation checklists, transportation, delivery, use and recovery records of the device, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies certified, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and subjects' files and records kept at the pharmacy, laboratories and ancillary departments involved in the clinical study. The AE and SAE Report Forms contain information other than medical records will be considered as the source document.

8.3.2 Direct Access

Each study site will maintain medical and study records for this study in compliance with the GCP for Medical Device Trials and regulatory and institutional requirements. In order to protect the safety, rights and interests of the subjects, to ensure the authenticity, accuracy and integrity of the study and data, each study site must allow Monitors, QA personnel, regulatory authorities and authorized representatives to have the right to access, review or verify source data or source documents.

8.3.3 Data Handling and Record Requirements

Data quality procedures are designed to ensure the complete, accurate and timely data are submitted in accordance with clinical protocol requirement. The data management plan will be completed after the clinical protocol is finalized and before the first subject is enrolled. Data management plans may need to be updated and revised according to actual operations.

8.3.4 Data Recording and Record Retention

Study records shall be stored properly to ensure the privacy, confidentiality, security and accessibility of the records during and after the conduct of the study. The Investigator/Institution will take measures to prevent accidental or premature destruction of those documents. The Investigator must retain essential study documents according to the local/regional regulations 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.

When the responsible Investigator retires, relocates, or withdraws from responsibility of keeping the study records, custody must be transferred to a delegated person. Smith & Nephew 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 Smith & Nephew.

8.4 STUDY ENDPOINTS

8.4.1 Primary Endpoint

The primary endpoint of the study is defined as proportion of excellent (≥ 90) or good (80-89) HHS scores at 12 month postoperative.

8.4.2 Secondary Endpoints

Safety and efficacy evaluated in this study at baseline, 6 weeks, 3 months, 6 months, 1 year and 2 years after surgery as measured by:

- Survivorship of the OR3O™ Dual Mobility System (no revision due to any reason)
- Survivorship of controlled system (no revision due to any reason)

- Harris Hip Score (HHS)
- EuroQol (European quality of life) five-dimensional Five-level (EQ-5D-5L) score
- Hip Disability and Osteoarthritis Outcome Score for Joint Replacement (HOOS JR.)
- Radiographic Assessment
  - Implant position/Orientation
  - Implant subsidence/migration
  - Periprosthetic fractures
  - Heterotopic ossification
  - Radiolucencies
  - Osteolysis
  - Implant loosening
  - Stress Shielding

8.4.3 Other Endpoints

The following exploratory endpoints will be collected:

- Dislocation percentage of the hip up to 2 years after device implantation.
- Hospital readmission percentage (cumulative) within 30, 60 and 90 days of discharge due to any reason related to study device or study procedure.

8.4.4 Safety Endpoints

Safety endpoints include the collection of the following events:

- All adverse events (AEs) occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events.
- Device Deficiencies.

8.5 Methods Used to Minimize Bias and Maximize Validity

8.5.1 Multiple Sites

Subjects will be enrolled at multiple sites, utilizing up to 4 sites in total for the study. This will reduce the effect of observer bias that might arise at any one study site as well as maximize the diversity of subjects treated.

8.5.2 Randomization

Subjects meet all inclusion/exclusion criteria will be randomly allocated into any of two study groups (study arm or controlled arm) in a 1:1 allocation ratio. Blocked randomization to balance this allocation ratio by investigational site and overall will be implemented through a network-based randomization system. A randomization number is allocated only when subjects have signed the Informed Consent Form and satisfy all study eligibility criteria.

8.5.3 Prospective Enrollment

Enrollment will be utilized to enroll subjects who meet the inclusion/exclusion criteria.

8.5.4 Balanced Covariates

The Inclusion/Exclusion criteria will be generalizable and applicable to the widest possible subset of the population satisfying the study's eligibility criteria. This should maximize the applicability to as many subjects with similar baseline characteristics and help to bolster external validity.

8.5.5 Subject Attrition

Subject attrition for the sample size has been accounted for in the estimate of the Confidence Interval (CI) so as to validate the analysis and most efficiently use the available subjects.

8.5.6 Pre-specification of Statistical Analysis

The primary outcome measure has been pre-specified as well as the type of statistical analysis to be performed in order to evaluate this outcome. The details of the analysis will further be pre-specified in the Statistical Analysis Plan (SAP) so as to minimize bias.

9. STUDY PROCEDURES

9.1 VISITS AND EXAMINATIONS

9.1.1 Summary

For a summary of the required procedures by visit, refer to the Study Schematic Table 9-1.

Table 9-1: Study Procedures by Visit

Schedule of events	Pre-Operative Data	Operative / Discharge	6 Weeks (42 – 7/+14 days)	3 mos (90 ±30 days)	6 mos (180 ±30 days)	1 yr. (365 ±60 days)	2 yr. (730 ±60 days)
Informed Consent	x						
Inclusion/ Exclusion	x						
Demographics	x						
Medical History	x						
Vital Signs	x						
Preoperative Lab Examinations (eg. Blood Routine Examination, Biochemical Examination, Coagulation Examination) [1]	x						
Pregnancy Test[2]	x						
Operative Data		x					
Discharge Data		x					
Implant status			x		x	x	x
HHS	x		x	x	x	x	x
EQ-5D-5L	x		x	x	x	x	x
HOOS JR.	x		x	x	x	x	x
Radiographic Assessment	(x)[3]	(x)[4]	(x)[4]	x	x	x	x
Concomitant Medications[5]		x	x	x	x	x	x
Safety Assessment (AEs, DDs)		x	x	x	x	x	x
End of Study/ Exit		x	x	x	x	x	x

1 If applicable, where, for preoperative lab examinations, only those within Day 0~14 before the operation are acceptable.

The Preoperative Lab Examinations required to be performed include:

- Blood routine examination: Haemoglobin, Platelet count, White Blood Cell count, neutrophil count, erythrocyte sedimentation rate
- Coagulation examination: Prothrombin time, activated partial thromboplastin time), thrombin time, D-dimer
- Biochemical examination: Urea or urea nitrogen, creatinine, AST, ALT, blood glucose
- Other examination: Erythrocyte sedimentation rate

2 If applicable, where, the pregnancy test is only suitable for females of child-bearing potential, neither premenstrual females nor sterilized or postmenopausal (i.e., 12-month amenorrhea without alternative medical reasons) females.

[3] If X-ray image has been done within 30 days before the Informed Consent Form is signed, and the data is available, they can be used as the data for screening before operation.

[4] Radiographic assessment performed at discharge or 6 weeks follow-up visit only.

[5] All combination medications associated with AEs or serious adverse events (SAEs) are reported.

9.1.2 Screening / Preoperative Visit

1. Obtain written informed consent from the subject as detailed in Section 7.5.

   ----- Do not proceed until consent has been obtained -----

2. Set up the subject in the electronic data capture system. Subject number will be assigned to subject.

3. Finalize subject screening by verifying all inclusion/exclusion criteria. Any subject who signs an ICF but fails to meet the entry criteria is considered to be a Screen Failure.

4. Obtain demographic information and relevant medical history, including information on all concomitant medications/therapies, as well as perform preoperative lab examination and radiology exam where applicable.
   Relevant medical history will be defined as anything that is active to include the indication for the THA (i.e. OA, RA, Fracture, AVN etc.), as well as anything related to the following conditions:
   - Cardiovascular Disease;
   - Pulmonary Disease;
   - Liver Disease;
   - Renal Disease;
   - Gastrointestinal Disease
   - Hematological Disease;
   - Endocrine Disorders;
   - Cancer;
   - Recent surgeries (within the last year);
   - Recent illness;
   - Previous surgeries on the affected hip.
   - Other pre-existing conditions that may lead to unrelated adverse events after study enrollment.

6. Complete the HHS.

7. Have the subject complete the EQ-5D-5L questionnaire.

8. Have the subject complete the HOOS JR questionnaire.

9. Review the pre-operative radiographic assessment as per standard of care to collect subject diagnosis information
10. Instruct the subject to return for the Operation Visit on the scheduled date.
11. Transcribe data to the eCRF.

9.1.3 Operation Visit (Day 0) / Discharge

1. Collect information on any changes in subject general health and the use of concomitant medications. Update medical history as necessary.
2. Perform surgery and collect intraoperative data on source documents. This includes but is not limited to the following information:
   - Implant product – study arm or controlled arm
   - Implant data
   - Surgical data e.g. duration, surgical approach
   - AEs, Device Deficiencies

   Any subject who signs an ICF but fails to be implanted with the study device for any reason is considered to be a Screen Failure.
3. At time of discharge, collect discharge data on source documents. This includes but is not limited to the following information:
   - Discharge Date
   - Mobility Status
   - Medication at discharge
   - AEs, Device Deficiencies
4. Based on standard of care at the study site, the investigator will decide whether the radiographic assessment will be performed prior to discharge or at the 6 weeks follow-up visit. Radiographic images are to be collected in anteroposterior (AP) and lateral view in supine position. Investigator to review the images and radiographic report, as well as record data in the subject's medical record.
5. Instruct the subject on follow-up procedures, including returning to the site for the follow-up visit in 6 weeks (42 days (- 7 days / +14 days) from the date of surgery).
6. Transcribe data to the eCRF.

9.1.4 Follow-Up visit at 6 weeks post-surgery (42 - 7 days / + 14 days from the date of surgery)

1. Query subject regarding any changes in general health and the use of concomitant medications. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies.
2. Verify with subject if any revision has occurred since last visit. If any revision is observed or reported, it must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies. Revised components are to be recorded.
3. Complete the HHS.
4. Have the subject complete the EQ-5D-5L questionnaire.
5. Have the subject complete the HOOS JR. questionnaire.
6. Collect radiographic images of the affected hip in AP and lateral view in supine position if not performed at discharge. Investigator to review the images and record data in the subjects' medical record.
7. Instruct the subject on returning to the site for the next follow-up visit.
8. In case the follow-up visit was missed, contact the subject by telephone to collect information on implant status and adverse events. Collect the information on the appropriate source document.
9. Transcribe data to the eCRF.

9.1.5 Follow-Up visits at 3 months (90 ±30 days), 6 months (180 ±30 days) and 1 year (365 ±60 days) post-surgery

1. Query subject regarding any changes in general health and the use of concomitant medications. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies.
2. Verify with subject if any revision has occurred since last visit. If any revision is observed or reported, it must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies. Revised components are to be recorded.
3. Complete the HHS.
4. Have the subject complete the EQ-5D-5L quesionnaire.
5. Have the subject complete the HOOS JR. questionnaire.

6. Collect radiographic images of the affected hip in AP and lateral view in supine position. Investigator to review the images and radiographic report, as well as record data in the subjects' medical record.
7. Instruct the subject on returning to the site for the next follow-up Visit.
8. In case the follow-up visit was missed, contact the subject by telephone to collect information on implant status and adverse events. Collect the information on the appropriate source document.
9. Transcribe data to the eCRF.

9.1.6 End of Study Visit 2 years post-surgery (730 ±60 days) or upon withdrawal from the study

1. Query subject regarding any changes in general health and the use of concomitant medications. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies.
2. Verify with subject if any revision has occurred since last visit. If any revision is observed or reported, it must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies. Revised components are to be recorded.
3. Complete the HHS.
4. Have the subject complete the EQ-5D-5L questionnaire.
5. Have the subject complete the HOOS JR. questionnaire.
6. Collect radiographic images of the affected hip in AP and lateral view in supine position. Investigator to review the images and radiographic report, as well as record data in the subjects' medical record.
7. In case the follow-up visit was missed, contact the subject by telephone to collect information on implant status and adverse events. Collect the information on the appropriate source document.
8. Transcribe data to the eCRF.
9. Complete End of Study eCRF.

9.1.7 Unscheduled Visits

Unscheduled examinations may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents. The reason for the unscheduled visit as well as implant status should be transcribed to the appropriate eCRF. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies. The subject should be scheduled to return for the next scheduled study visit within the acceptable time window.

9.1.8 Concomitant Medications and Therapies

Concomitant medications and concomitant therapies after surgery are recorded at any time from enrollment into the study through the subject's last study visit.

9.1.8.1 *Concomitant Medications*

Excluded Concomitant Medications

There are no restrictions on concomitant medications for this study.

Recording Concomitant Medications in the eCRF

Only medications related to the study treatment and medications used to treat an adverse event related to the study device and / or study procedure and device deficiency will be recorded in the eCRF. Reference the eCRF Completion Guidelines for additional information.

9.1.8.2 *Concomitant Therapies*

Therapies Prohibited During the Study

There are no restrictions on concomitant therapies for this study.

Recording Concomitant Therapies in the eCRF

Only therapies related to the study treatment and therapies used to treat an adverse event related to the study device or study procedure and device deficiency will be recorded in the eCRF. Reference the eCRF Completion Guidelines for additional information.

9.1.9 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are lost to follow-up or who are withdrawn from the study for any reasons (refer to section 7.7 and 7.8 for further details). Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation (if given by the subject) should be captured (see Section 7.8.3).

Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

9.1.10 Subject Pregnancy

Women who are pregnant or breast feeding are excluded from the study. However, if a woman becomes pregnant during the study, Smith+Nephew must be contacted immediately once the investigator is made aware of the pregnancy. All study procedures that are contraindicated during pregnancy and/or lactation (e.g. radiographic examinations) will not be required. A decision will be made regarding the continuation in the study of the pregnant woman. Pregnancy is not an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until the end of the pregnancy.

9.2 Study Methods and Measurements

9.2.1 Survivorship

Survivorship of THA is defined as no revision of any of the components of the OR3O™ Dual Mobility System (insert, liner) or controlled product, acetabular shell, femoral head and femoral stem. Information on implant / component survivorship will be derived from adverse event in eCRFs.

9.2.2 Harris Hip Score

The Harris Hip Score (HHS) will be collected before surgery and at 6 weeks, 3 months, 6 months, 1 year and 2 years after surgery.

The Harris Hip Score is a joint specific score that consists of 10 items covering domains of pain (1 item, 0-44 points), function (7 items, 0-47 points), functional activities, absence of deformity (1 item, 0 or 4 points), and hip range of motion (2 items, 0-5 points). Scores range from 0 (worst) to 100 (best).

9.2.3 Radiographic Assessment

An AP and a lateral view radiograph are required to adequately assess the status of the study device. Radiographs are taken during the course of the study at discharge or 6 weeks, 3 months, 6 months, 1 year and 2 years after surgery. Radiographs will be performed with the subject in a supine position.

Assessments to be made from radiographs will include:

- Implant position/Orientation
- Implant subsidence/migration
- Periprosthetic fractures
- Heterotopic ossification
- Radiolucencies
- Osteolysis
- Implant loosening
- Stress Shielding

Images taken at discharge or 6 weeks after surgery will serve as baseline for comparing subsequent images. Information on initial implant position will also be collected from the baseline images.

In addition, pre-operative radiographs are obtained to evaluate the initial disease diagnosis. Images can be used that have been taken according to the methodology and timing that is standard of care at each site as long as the radiographs are taken within 30 days prior to surgery.

Radiographic images and reports will be reviewed by the Investigator, data will be recorded in the subjects' medical chart. Subsequently information will be transcribed to the radiographic part in eCRFs.

9.2.4 Dislocation of the hip

The dislocation information of the hip will be collected up to 2 years after device implantation. Information on dislocation of the hip will be derived from the adverse event eCRFs.

9.2.5 Hospital readmission

The hospital readmission information will be assessed at 30, 60 and 90 days after discharge. Information on hospital readmission will be derived from the adverse event eCRFs.

9.3 HEALTH ECONOMICS/QUALITY OF LIFE

9.3.1 EQ-5D-5L

The EQ-5D-5L questionnaire will be collected before surgery, at 6 weeks, 3 months, 6 months, 1 year and 2 years after surgery. A paper questionnaire will be provided by the Sponsor to be completed by the subject. Subsequently the information will be transcribed to the eCRF.

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ VAS.

The descriptive system is used to describe the subject's health state and consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels to choose the most appropriate answer: no problems, slight problems, moderate problems, severe problems and extreme problems. The subject is asked to indicate his/her health state by marking the most appropriate statement in each of the five areas.

The EQ VAS records the subject's self-rated health on a vertical visual analogue scale. The endpoints on the scale are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome as judged by the individual respondents.

9.3.2 Hip Disability and Osteoarthritis Outcome Score for Joint Replacement (HOOS JR.)

The HOOS JR. questionnaire will be collected before surgery, at 6 weeks, 3 months, 6 months, 1 year and 2 years after surgery. A paper questionnaire will be provided by the Sponsor to be completed by the subject. Subsequently the information will be transcribed to the eCRF.

The HOOS JR. is a short-form survey based on the HOOS that specifically focuses on the outcome after THA. HOOS JR. consists of 2 areas: pain (2 items) and function, daily living (4 items). The last week is taken into consideration when answering the questions. Standardized answer options are given (5 Likert boxes – no, mild, moderate, severe, extreme) and each question gets a score from 0 to 4. An interval score from 0 -100 (0 indicating total hip disability and 100 indicating perfect hip health) is calculated (15) .

10. STATISTICAL DESIGN

A SAP that will provide more detailed and precise information on the study's analyses will be written and finalized prior to database lock.

10.1 GENERAL

Smith & Nephew's Biostatistics group or an assigned vendor including the AOANJRR will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals (CI) will be generated where appropriate. Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum and maximum values.

All statistical comparisons of data would describe the test statistic used as well as its distributional assumptions. For continuous variables, in an event of marked deviation from normality assumptions, a commensurate non-parametric test will be used as alternative thereby eliminating the possibility of violation of normality assumptions. All analyses will be performed using SAS™ version 9.3 (or a later version).

10.2 ANALYSIS POPULATIONS

The following section details the analysis populations:

- Safety (SAF) Population: This is defined as all hips who have been implanted with the OR3O™ Dual Mobility System or controlled system.

- Full Analysis Set (FAS) Population: according to the basic principle of Intent-to-Treat (ITT) analysis, all randomly selected subjects with at least one validity evaluation will be included in FAS Population.
- Per-Protocol (PP) Population: The PP population is a subset of hips in the FAS population who do not have major protocol deviations and who satisfied all enrollment eligibility criteria. Criteria that can be regarded as major deviations will be formally classified on a case-by-case basis prior to the final study database lock.

10.3 BASELINE DATA

All observations available prior to the operative date will be defined as baseline data. All demographic and preoperative characteristics data will be summarized at baseline. All demographic and baseline characteristics will be summarized using the SAF, ITT and PP analysis populations.

Demography and medical variables at baseline (including but not limited to, age, gender, race, medical history, medical history and disease diagnosis) will be used to describe subjects and summarize subject information. Summary statistics will be given based on the nature of variables (continuous or classified variables). For continuous variables, the number of observations, mean, standard deviation, median, minimum and maximum will be reported. For classified variables, the number of observations, frequency and percentage will be reported.

A detailed list of different data set sizes in each group, case distribution of each site, total dropout rate comparison and reasons for not completing the study, will be provided. The demographic characteristics (age, height, vital signs, etc.), the medical history and the medication history of the patients are described, and comparison of the age, height, body weight, etc. between the two groups will be conducted to measure the comparability between the two groups. The outcome data can be accepted and reported only when the baseline of two groups is balanced; otherwise, the outcome data needs to be corrected and then can be reported.

10.4 EFFICACY ANALYSIS

10.4.1 Analysis of Primary Endpoint

The primary endpoint of this study is the proportion of excellent (≥ 90) or good (80-89) HHS scores at 12 month postoperative. Hypothesis testing would be in two steps. First, testing for non-inferiority of P1 versus P0 and secondly if non-inferiority is demonstrated then testing for superiority of P1 to P0 as follows:

H0 (null): P1 ≤ (P0-Δ) versus

Ha1 (alternate 1st stage): P1 > (P0-Δ) and Ha2 (alternate 2nd stage): P1 > P0,

Where Δ is the margin of non-inferiority (9.5%), P1 is the proportion of good to excellent HHS scores at 12 months in the OR3O dual mobility system (test) and P0 is the proportion of good to excellent HHS scores at 12 months in the Conventional, single-bearing design (control).

- The null hypothesis, H0, is rejected in favor of the first alternate hypothesis, Ha1, (i.e. demonstration of non-inferiority) if the lower limit of the 95% Confidence interval for P1 > (P1-Δ) otherwise, H0 will be accepted.
- If the null hypothesis, H0, is rejected in favor of Ha1, the test for superiority would additionally be performed. If the upper limit of the 95% CI for P0 is less than the lower limit of the 95% CI for P1, then superiority of P1 to P0 is demonstrated, i.e. acceptance of Ha2.. This stepwise hypothesis-testing framework would not require any adjustment made to α, thus strongly controlling the overall significance at 0.05. All 95% CIs generated for P1 and P0 would be calculated using exact methods.

The primary endpoint will be summarized using the ITT population as the primary analysis population and then subsequently with the per PP population for sensitivity analysis.

10.4.2 Analysis of Secondary Endpoints

<u>Implant Survivorship</u>

- Survivorship of the OR3O Dual Mobility System (assessed by revision for any reason) will be summarized using Kaplan-Meier survival tables and graphs. Time to revision will be the endpoint of interest, for subjects who die, are lost to follow-up or do not encounter the event of interest by the time of study termination would be censored on these dates.

- Survivorship of the controlled system up to 2 years after surgery (assessed by revision for any reason). Kaplan-Meier survival tables analogous to that specified for the OR3O Dual Mobility system will be implemented here as well.

Harris Hip Score (HHS)

- HHS scores for each subject will further be categorized as follows: Excellent (90-100); Good (80-89); Fair (70-79); Poor (60-69) and; Very poor (<60). Shift tables from the preoperative visit to all postoperative visits using these classifications will be generated.
- The total HHS and the scores for each of its following subdomains: pain, function, absence of deformity, and range of motion will be summarized using continuous summary characteristics preoperatively and postoperatively at 6 weeks, 3 months, 6 months, 1 year and 2 years (i.e. by visit). For the HHS and its subdomain scores, independent repeated measures Analysis of Covariance (ANCOVA) model (with visit as the repeated term) will be used to model the change from preoperative to postoperative total HHS (and its subdomain) scores as dependent variable (s). As a minimum, each model will contain treatment (OR3O dual mobility system i.e. Test, versus Conventional single-bearing design, i.e. Control) as a fixed term and a repeated specification for visit in the model. Preoperative prognostic and demographic variables including but not only restricted to type of THA procedure (primary), age, BMI, sex, and investigational site and any other covariate that can be ascertained to be impactful on the total HHS (or its subdomain scores) will be introduced as covariates in the final model. These covariates will be added to the model in a stepwise manner and retained in the final model if a p-value of $\leqslant$ 0.1 is encountered. Model based means (adjusted means or Least Square Means, LSMeans) and corresponding standard errors associated with the change from preoperative to postoperative HHS (and its subdomain) scores by treatment will be presented. Model based differences (and corresponding standard errors) between treatment as well as their corresponding 95% CIs will additionally be summarized. If the p-value associated with the treatment term in the model is significant (i.e. $p < 0.05$).

EQ5D-5L Score

- The HRQoL Index score and its VAS component will be sumarized using summary statistics for continuous variables preoperatively and at the postoperative visits: 6 weeks,

3 months, 6 months, 1 year and 2 years (i.e. by visit). Model based repeated measures ANCOVA analysis, the type specified for the total HHS and its subdomain scores will be implemented.

Hip Disability and Osteoarthritis Outcome Score for Joint Replacement (HOOS JR.)

- The HOOS JR. scoring instrument that will be administered for this study has two dimensions (pain and function, daily living). Pain has 2 items scored and function, daily living has 4 items with a combined 6 total items. Each of the items within each dimension has a rating of 0-4 where 0 is the best outcome on the item and 4 is the worst outcome on the item. The maximum HOOS JR raw summed score for all dimensions combined is 24. The higher the combined raw scores is the worse the outcome. The raw summed scores are transformed to a 0-100 interval score where a score of 0 implies total hip disability and a score of 100 signifies perfect hip health. The scoring instructions for the transformation will be detailed in the SAP. Thetransformed (0-100) interval scores will be summarized by visit using descriptive summary characteristics for continuous variables preoperatively and at the postoperative visits: 6 weeks, 3 months, 6 months, 1 year and 2 years (i.e. by visit). Changes from preoperative to postoperative follow-up time points will similarly be summarized. Model based repeated measures ANCOVA analysis, the type previously specified for the total HHS (and its subdomain scores) will be implemented.

Radiographic Characteristics

- The radiographic characteristics of implant position, implant fixation, heterotopic ossification, radiolucencies, osteolysis, atrophy and hypertrophy will be summarized using descriptive characteristics for continuous or categorical variables as appropriate and relevant.

All secondary endpoints will be summarized using the ITT analysis population.

10.4.3 Analysis of Other Endpoint(s)

Survivorship of compatible components up to 2 years

Survivorship of acetabular shell, femoral head, and any of the femoral stems will be estimated by cumulative proportion of hips without revision of the respective components due to any reason, up to 2 years. The cumulative implant survival rates will be summarized using KM product limit estimates.

Dislocation percentage of the hip up to 2 years after device implantation

The cumulative dislocation percentage at the interim visits up to 2 years after device implantation, $p_{dis,i}$ will be compared to a literature specified percentage, $p_{literature}$. These literature-specified percentages will be included in the SAP created for the study. For the estimation of dislocation rate, a hip with multiple dislocations on-study will be counted only once. Two-sided exact 95% CIs will be estimated for $p_{dis,i}$ where i is the visit at which the cumulative dislocation will be estimated (i.e. at 3months, 6 months, 1 year and 2 years).

One of the following conclusions will be made:

- If the lower limit (LL) of the 95% CI for $p_{dis,i}$ is > $p_{literature}$, then it is concluded that the dislocation rate on-study is significantly greater than the literature-specified rate.
- If the upper limit (UL) of the 95% CI for $p_{dis,i}$ > $p_{literature}$, then it is concluded that the dislocation rate on-study is significantly less than than the literature-specified rate.
- If (LL of 95% CI of $p_{dis,i}$ <= pliterature <= UL of 95% CI of $p_{dis,i}$), then the dislocation rate on-study is comparable to that specified in literature.

Hospital readmission percentage (cumulative) within 30, 60 and 90 days of discharge

The readmission percentage by 30, 60 and 90 days of discharge, p30,60,90 will be descriptively summarized as counts (n) and percentages (%).

10.5 SAFETY ANALYSES

- The number of adverse events will be reported both overall and by seriousness, relationship to study device and/or study procedure and expectedness.
- The number of subjects experiencing adverse events will be summarised both overall and by seriousness, relationship to study device and/or study procedure and expectedness.
- An overall AE summary table that will summarize as number (n) and percentages (%), the overall incidence according to subjects with at least one AE; subjects with at least one AE by worst severity (mild, moderate, or severe); subjects with at least one AE by worst

outcome (resolved, ongoing/unresolved, or death); subjects with an AE that led to study discontinuation and; subjects with at least one AE by worse relatedness to device. Other events such as SAEs, ADEs, SADEs or USADEs will also be similarly summarized using number (n) and percentages (%).

- Incidence of device- or procedure-related re-interventions that occur on-study will be summarized as number (n) and percentages as well as by type.
- A listing of device deficiencies that occur on-study will be provided.

All safety endpoints will be summarized using the SAF analysis population.

10.6 INTERIM ANALYSES

An interim analysis is planned for after completion of all 1 year follow-up visits in order to support the China NMPA registration. Additional interim analyses might be performed as and when needed to support and maintain product registration in different markets globally. More specific details on the interim analyses will be included in the SAP.

11. SAMPLE SIZE JUSTIFICATION

11.1 TOTAL SAMPLE SIZE

170 subjects who need unilateral hip joint replacement should be enrolled into the study - 85 subjects randomized per study arm.

The primary assumptions for sample size calculation are as below:

- Type I (α) error = 0.05
- Type II (β) error = 0.20 (Power = 80%)
- Margin of non-inferiority, Δ = -9.50%

Sample size calculation is based on the assumption that in order to be considered of comparable efficacy, study arm (dual mobility cohort) must obtain at least 90% of the efficacy in the controlled arm (conventional cohort). It is expected and further assumed that 95% of the Harris Hip Score at 12 months postoperative will have a rating of good or excellent (80-89, $\geqslant$ 90), then 76 evaluable subjects per group would be required to carry out the hypothesis testing at 12 months postoperatively. Assuming an attrition rate of 10% at 1 year, 85 subjects are needed per arm. It is

planned to have 4 sites enrol on average, 43 subjects per investigational site and a min. of 20 subjects should be enrolled per site (overall subjects enrolled in the study of 170).

11.2 NUMBER OF SUBJECTS WITH EACH DISEASE IN CLINICAL STUDY AND REASON FOR DETERMINATION

In this clinical protocol, it is strictly required that patients should be enrolled in compliance with the inclusion/exclusion criteria. It can be considered that all the patients have the same type of disease, and are not further divided.

11.3 IN MULTI-CENTER CLINICAL STUDY, MINIMUM AND MAXIMUM NUMBER OF SUBJECTS IN EACH CLINICAL STUDY INSTITUTION AND JUSTIFICATION

This study will be carried out at the same time in a number of clinical study sites. In principle, the number of subjects enrolled in each site will be distributed as evenly as possible to ensure adequate site representation. However, considering the feasibility and progress of the enrolment, the number of subjects enrolled will be adjusted according to the actual situation to ensure that the enrolment scale at each site is relatively balanced, and that the final enrolment scale for a specific site should not exceed 50% of the total number of cases.

11.4 SIGNIFICANCE LEVEL AND POWER OF THE CLINICAL STUDY

The statistical significance level takes the two-tailed significance level of $\alpha = 5\%$, 80% power $(1-\beta)$.

11.5 EXPECTED DROP-OUT RATE

Expected drop-out rate is not more than 10%.

11.6 CRITERIA FOR ACCEPTABILITY/UNACCEPTABILITY OF CLINICAL STUDY RESULT

Primary efficacy endpoint (the Proportion of excellent ($\geqslant$ 90) or good (80-89) HHS scores at 12 months postoperative): If the lower limit of 95% CI for the efficacy difference between two groups is greater than the non-inferiority margin, it is considered that the investigational product is non-inferior to the control product, the statistical hypothesis is valid and the result of clinical

trial is qualified; otherwise, the hypothesis is invalid, and the result of clinical trial is unacceptable.

11.7 CRITERIA AND REASON FOR TERMINATING THE STUDY BASED ON THE STATISTICAL CONSIDERATION

Interim analyses will be performed after completion of all 1 year follow-up visits.

11.8 STATISTICAL METHOD OF ALL DATA, TOGETHER WITH THE HANDLING METHOD OF MISSING, UNUSED AND WRONG DATA (INCLUDING DISCONTINUATION AND WITHDRAWAL) AND UNREASONABLE DATA

The statistical analysis plan will be finalized prior to the study's database lock. The statistical analysis programming and logic test programming will be conducted according to the statistical analysis plan. Draft tables, figures and listings would be generated prior to database lock using dummy assigned treatment codes. A data review meeting may be convened prior to the database lock to determine major and minor protocol deviations.

Missing data on the primary endpoint would be imputed using the Last Observation Carried Forward (LOCF) single value imputation method.

11.9 REPORTING PROCEDURE OF DEVIATION FROM ORIGINAL STATISTICAL PLAN

In the event of a change to the statistical analyses indicated in the clinical protocol, the change procedure shall be applied in advance, such as changes in the statistical plan shall be truthfully recorded in the statistical analysis plan, including changed position, change reasons, change time and other revision records.

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

The categories of adverse events are shown in Table 12-1. The definitions for each of these categories are given in the subsequent sections.

Table 12-1: Categories of Adverse Event

	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 12.1.3)	
		ANTICIPATED	**UNANTICIPATED**
		ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)	UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not causally related to the IP/Ancillary Product and whether anticipated or unanticipated.

Any events that occur newly or deteriorate in severity and frequency as compared with baseline conditions, or abnormal results found in the process of diagnosis, including abnormal laboratory findings, are included herein.

Note 1: This definition includes events related to the IP, comparator or ancillary products.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the IP

AE is used both to refer to AE which do not meet the definitions of Adverse Device Effects or Serious Adverse Events and as an umbrella term referring to adverse events of all classifications.

An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease. For reporting purposes, emphasis is placed first and foremost on whether or not the event constitutes an untoward medical occurrence.

12.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event that is related to the use of the IP.

Note 1: 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.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes "comparator" if comparator is a medical device.

Not Related - An AE is considered to be not related to the use of an IP or the procedure when the effect is DEFINITELY UNRELATED to the use of the IP or the procedure;

Related – An AE is considered to be related to the use of an IP or the procedure when there is a POSSIBLE or DEFINITE relationship between the AE and the use of the IP or the procedure.

An ADE is further categorized depending on whether the criteria in section 12.1.3 and 12.1.4 are met.

12.1.3 Serious Adverse Events and Serious Adverse Device Effects

An AE or ADE is considered a **Serious** Adverse Event (SAE) or **Serious** Adverse Device Effects (SADE) if, in the view of either the Investigator or the Sponsor, it:

a) led to death,

b) led to serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, 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,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

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

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

An unanticipated Serious adverse device effect (USADE) is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Guidance Regarding the Determination of Unanticipated Events:

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Instruction for Use, the Clinical Protocol or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

12.1.5 Severity

The severity of every AE will be assessed by the PI or medically qualified site staff to whom the responsibility has been delegated and documented on the delegation of authority log. AE should be classified as mild, moderate, or severe, regardless of whether or not the AE are considered to be serious or non-serious. The classification should be based on the following definitions:

Mild - An event is mild if the subject is aware of, but can easily tolerate the sign or symptom;

Moderate - An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities;

Severe - An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

12.1.6 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DD includes malfunctions, use errors and inadequate labeling.

Note 1: DD includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

12.2 AE Coding Dictionary

Coding for this study will be done per International Medical Device Regulators Forum AE Terminology Annex E – Clinical signs, symptoms and conditions.

12.3 Reporting Procedures

AE of any kind and DD will be recorded in the applicable eCRF and source notes. The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity. DD

will be evaluated for potential to cause SADE. The following timescales should be followed for the AE/DD information to be entered into the eCRF and reported to the Sponsor or designee (see Figure 12-1):

- 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)

In case the electronic data capture system using eCRFs has a system down time for any reason, AEs should be reported to the Sponsor via e-mail to ensure timescales given above are met.

For ADE and DD, 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 Smith & Nephew unless it is contaminated (e.g., used dressings must not be retained). Updates to submitted information will be recorded in the eCRF according to the timescales above.

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. Adverse Event review will be performed according to the Sponsorś procedure.

The investigator will inform the IRB/EC of adverse events according to the IRB/EC requirements.

Depending on the nature of the adverse event, Smith & Nephew may request copies of the subject's de-identified 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, Smith & Nephew 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, SADE, USADE, and DD.

Figure 12-1: Evaluation and Reporting of AE

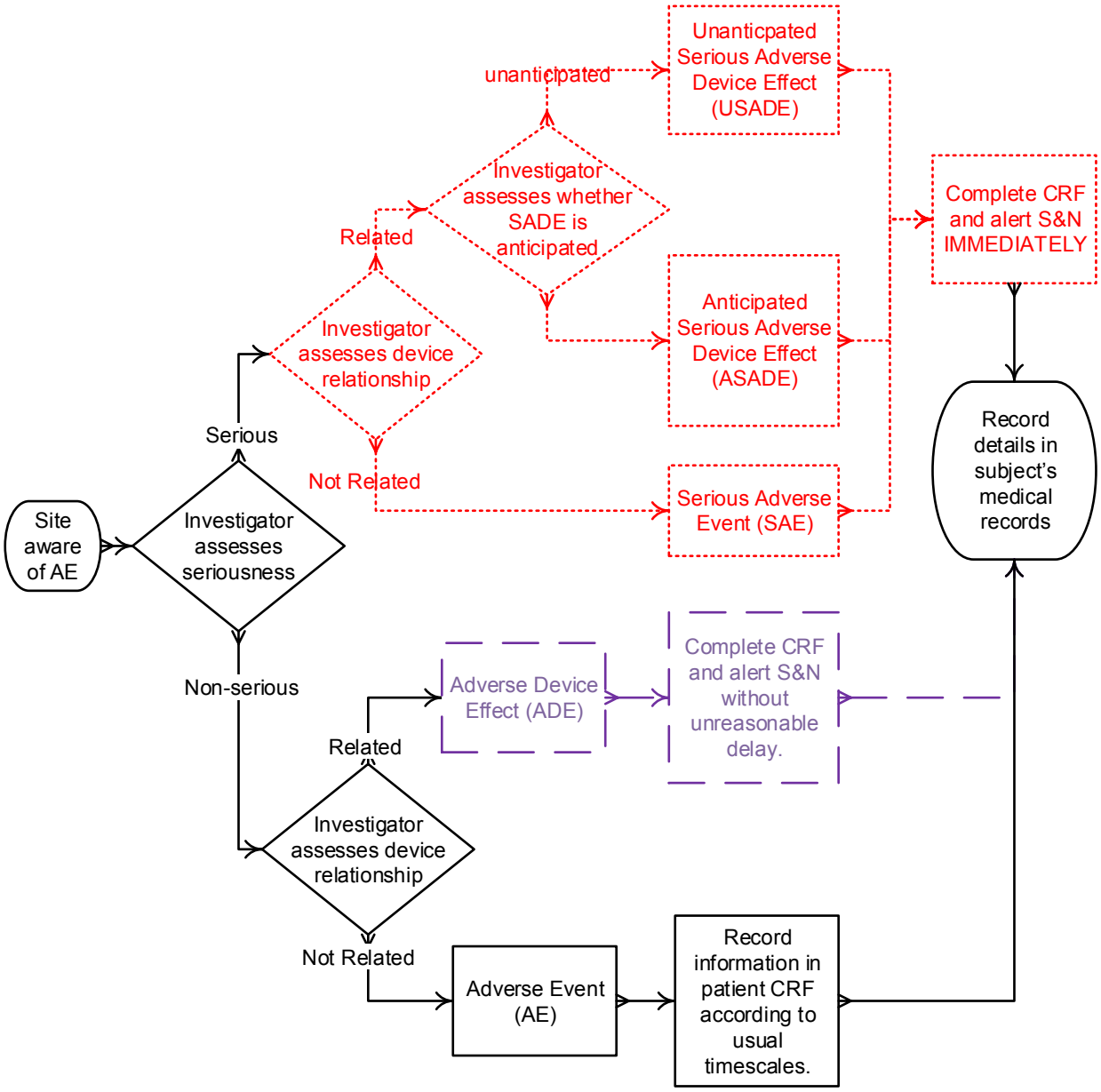
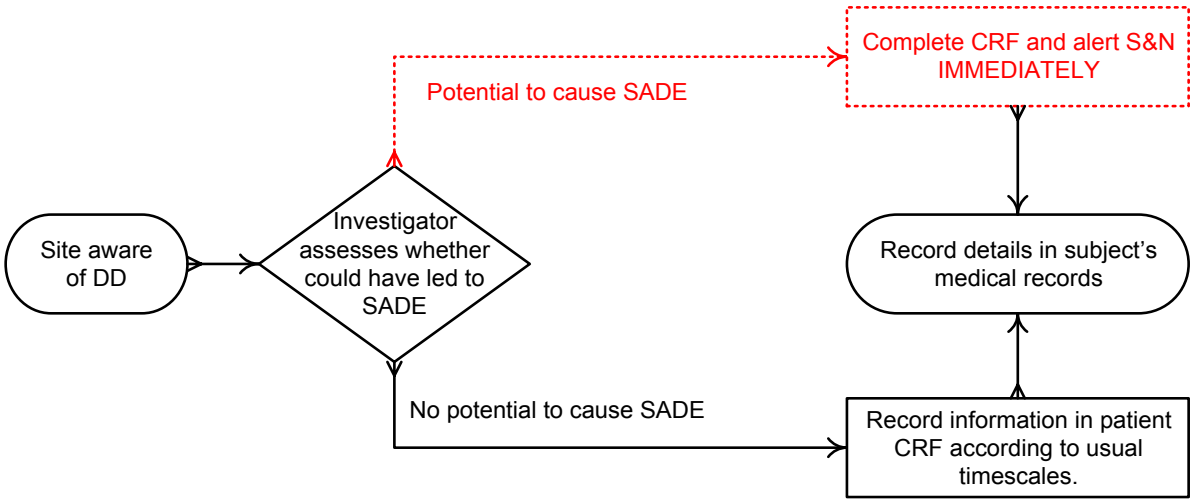


Figure 12-2: Evaluation and Reporting of DD



12.4 UNBLINDING OF INVESTIGATIONAL PRODUCT

Not applicable

12.5 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit to determine the outcome of the event.

Any additional data must be documented and available to the Sponsor who will determine whether the data needs to be documented in the eCRF or Clinical Study Report.

12.5.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or S+N IP and are ongoing at the end of subject's participation: The event should be followed until it is either resolved or until the event has become chronic and is not expected to further improve based on Investigator's review of the event.

Adverse events which are **not related** to a study procedure or S+N IP and are ongoing at the end of subject's participation should be followed for 30 days after discontinuation or if the AE is resolved, whichever is sooner.

At the time of data analysis (e.g., interim or final), an evaluation of ongoing events should take place and be listed as ongoing in the safety table.

13. INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with Good Clinical Practice (GCP) and all applicable regulatory requirements as outlined in Appendix 24.4 of this protocol.

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, at the end of 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.

14. SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate monitors to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the currently approved protocol and amendment(s), if applicable, with GCP regulations, and with applicable regulatory requirements.

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study.

14.1 SITE QUALIFICATION VISIT

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

14.2 ETHICAL APPROVAL AND CLINICAL TRIAL AGREEMENT

The clinical protocol and informed consent materials that used in the study must be approved by the EC. Copies of EC approval documents will be provided to Smith & Nephew.

A CTA must be fully executed by the site and Smith & Nephew and any other appropriate parties. Prior to initiation of the study, all investigators who will participate in the study need to be authorized by the principal investigator (PI), and the authorization outlines the responsibilities associated with the study. Unauthorized investigators are not allowed to participate in the study.

14.3 SITE INITIATION VISIT

A site initiation visit to provide training on the specifics of the study, site obligations and expectations of study conduct will be performed by the Sponsor or qualified person designated by the Sponsor.

14.4 INTERIM MONITORING VISIT

Interim monitoring visits will be performed by the Sponsor or qualified person designated by the Sponsor on a regular basis.

14.5 SPONSOR AUDITS AND REGULATORY INSPECTION

The objective of audit is to ensure the quality, authenticity and integrity of the clinical study and data, to ensure the risk of the study is controllable and evaluate whether the implementation of the study is strictly in accordance with the clinical protocol and SOP.

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

Due to the purpose of the study to support product registration, NMPA inspections of study conduct at clinical sites might occur.

14.6 CLOSE-OUT VISIT

A study close-out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, review IP accountability documents including documentation of return of unused devices, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements regarding records retention and EC reporting requirements. When no subjects have been included, a remote close-out visit may be conducted.

15. PROTOCOL DEVIATIONS

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Protocol deviations reported by the Investigator or discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (TMP-CD-31-02 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (TMP-CD-31-01 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and and signed off by the study personnel.

16. PROTOCOL AMENDMENTS

Amendments shall 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 EC. Protocol amendments need to be approved by the EC and Regulatory Authority(ies), 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 (CTA).

18. STATEMENTS OF COMPLIANCE

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; and Good Clinical Practice, as well as applicable national laws and requirements.

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

Public/Products Liability Insurance has been purchased by Smith & Nephew Worldwide and incorporates coverage for personal injury in respect of clinical studies. Smith & Nephew agrees to operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.

19. EHTICAL CONSIDERATION

This clinical study must follow the Declaration of Helsinki, and will be carried out according to the GCP and regulations related to medical devices issued by International conference on Harmonization (ICH) and China.

Investigators are responsible for obtaining written and dated approval from an Ethics Committee (EC) prior to enrolling subjects. This approval must include the protocol, the informed consent form, subject recruitment materials, advertising or any written information that will be provided to subjects.

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

In any event of withdrawal of EC Approval, the Investigator will report to the Sponsor within 5 working days if, for any reason, the EC withdraws approval to conduct the clinical study. The report will include a complete description of the reason(s) for which approval was withdrawn.

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

- Protocol amendments (should not be implemented prior to EC 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 report
- Adverse events described in Section 12 of this protocol
- All other documents as required by the EC

20. END OF STUDY

The end of the study is defined by the last follow-up visit that occurred in the whole study population. Due to defined visit windows the last follow-up visit must not necessarily be of the last subject treated.

Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g., safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g., departure of Investigator, non-compliance), then this will be undertaken according to the SOPs of the Sponsor.

The Sponsor may decide to discontinue a specific study site under the following conditions:

- Non-compliance to GCP or protocol
- Failure to enroll subjects
- Unsafe or unethical practices.

21. PUBLICATION POLICY

21.1 PUBLICATION OF STUDY DATA

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.

21.2 DATA SHARING

Smith & Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical studies. 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.

22. FEASIBILITY ANALYSIS

22.1 POSSIBILITY ANALYSIS ON SUCCESS

Smith & Nephew is a leading medical product enterprise and has a complete research and development (R&D), production and quality control (QC) system. The OR3O™ Dual Mobility System and similar products developed by Smith & Nephew have been marketed and used in foreign countries.

The material and design of the investigational product in this study meets the technical requirements of national registration and testing, the product has passed the testing of Quality Supervision and Inspection Center for Medical Devices successfully, and all the performance indicators are qualified.

The design of this clinical protocol is in accordance with Guidance for Clinical Trial Design of Medical Devices, and is repeatedly discussed and demonstrated by clinical experts, clinical study sites, statisticians and internal experts of Smith & Nephew.

The clinical sites that undertake this study have complete instruments, equipment and technical resources, and have passed the national certification for qualifications of clinical study sites. The investigators are outstanding academic leaders in the field of domestic sports medicine, with rich experience in clinical study, and can guarantee the smooth progress of clinical study.

22.2 POSSIBILITY ANALYSIS ON FAILURE

In the previous similar studies, most of the subjects were older patients. During the early follow-up of the study, due to the limitation of functional recovery of patients after surgery, there was a phenomenon of loss to follow-up. In view of this problem, according to the Guidance for Clinical Trial Design of Medical Devices, the follow-up time is arranged scientifically, which not only ensures that the early recovery data of subjects can be collected completely in the study, but also fully considers the convenience of subjects' actions. In order to avoid the loss to follow-up of subjects, in the informed consent process, the investigator’s team will fully emphasize the necessity for follow-up and the importance of protocol compliance with the subjects, allowing the subjects to fully understand the study procedures, and ensure the integrity of the adverse event collection of subjects during the study, at the same time repeatedly confirm and remind the follow-up arrangements of subjects in advance, and give compensation for the transportation cost from an ethical perspective.

Rating scale is a subjective evaluation index; in order to ensure consistency, each site will delegated individual evaluator, who are given consistency training according to scoring criteria.

The grasp of inclusion and exclusion criteria is the key to the success of the study. Smith & Nephew will provide sufficient training and the reminder cards to the investigators at the

beginning of the study. After the first subject is enrolled in each site, the Study Monitor will conduct a visit to the study site to verify the process are in line with the protocol requirements.

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24. APPENDICES

24.1 PROTOCOL AMENDMENT

Not applicable; this protocol has not been amended.

24.2 INSTRUCTIONS FOR USE

Instructions for Use (IFU) are made available for these implants. Refer to the most recent IFU for more information.

Instruction for Use Document ID 81104400

24.3 EQUIPMENT AND SPECIAL INSTRUCTIONS

The following section provides a list of components that are allowed to be used within the study:

Table 24-1: OR3O™ Dual Mobility Liners

Catalog Item #	Catalog Item Description
71358251	OR3O™ Dual Mobility Liner 32/44
71358252	OR3O™ Dual Mobility Liner 34/46
71358201	OR3O™ Dual Mobility Liner 36/48
71358202	OR3O™ Dual Mobility Liner 38/50
71358203	OR3O™ Dual Mobility Liner 40/52
71358204	OR3O™ Dual Mobility Liner 42/54
71358205	OR3O™ Dual Mobility Liner 44/56
71358206	OR3O™ Dual Mobility Liner 44/58
71358207	OR3O™ Dual Mobility Liner 46/60
71358208	OR3O™ Dual Mobility Liner 48/62
71358209	OR3O™ Dual Mobility Liner 50/64
71358211	OR3O™ Dual Mobility Liner 52/66-70
71358212	OR3O™ Dual Mobility Liner 54/72-74

Table 24-2: OR3O™ Dual Mobility Inserts

Catalog Item #	Catalog Item Description
71358253	OR3O™ Dual Mobility XLPE Insert 22/32
71358254	OR3O™ Dual Mobility XLPE Insert 22/34
71358213	OR3O™ Dual Mobility XLPE Insert 22/36
71358214	OR3O™ Dual Mobility XLPE Insert 22/38
71358215	OR3O™ DUAL MOBILITY XLPE INSERT 28/38
71358216	OR3O™ Dual Mobility XLPE Insert 22/40
71358217	OR3O™ Dual Mobility XLPE Insert 28/40

Catalog Item #	Catalog Item Description
71358218	OR3O™ Dual Mobility XLPE Insert 28/42
71358219	OR3O™ Dual Mobility XLPE Insert 28/44
71358221	OR3O™ Dual Mobility XLPE Insert 28/46
71358222	OR3O™ Dual Mobility XLPE Insert 28/48
71358223	OR3O™ Dual Mobility XLPE Insert 28/50
71358224	OR3O™ Dual Mobility XLPE Insert 28/52
71358225	OR3O™ Dual Mobility XLPE Insert 28/54

Table 24-3: Acetabular Shells – R3™ non-HA Acetabular Shells

Catalog Item #	Catalog Item Description*
71331848	R3™ No-Hole Acetabular Shell 48mm OD
71331850	R3™ No-Hole Acetabular Shell 50mm OD
71331852	R3™ No-Hole Acetabular Shell 52mm OD
71331854	R3™ No-Hole Acetabular Shell 54mm OD
71331856	R3™ No-Hole Acetabular Shell 56mm OD
71331858	R3™ No-Hole Acetabular Shell 58mm OD
71331860	R3™ No-Hole Acetabular Shell 60mm OD
71331862	R3™ No-Hole Acetabular Shell 62mm OD
71331864	R3™ No-Hole Acetabular Shell 64mm OD
71331866	R3™ No-Hole Acetabular Shell 66mm OD
71331868	R3™ No-Hole Acetabular Shell 68mm OD
71335548	R3™ Three Hole Acetabular Shell 48mm OD
71335550	R3™ Three Hole Acetabular Shell 50mm OD
71335552	R3™ Three Hole Acetabular Shell 52mm OD
71335554	R3™ Three Hole Acetabular Shell 54mm OD
71335556	R3™ Three Hole Acetabular Shell 56mm OD
71335558	R3™ Three Hole Acetabular Shell 58mm OD
71335560	R3™ Three Hole Acetabular Shell 60mm OD
71335562	R3™ Three Hole Acetabular Shell 62mm OD
71335564	R3™ Three Hole Acetabular Shell 64mm OD
71335566	R3™ Three Hole Acetabular Shell 66mm OD
71335568	R3™ Three Hole Acetabular Shell 68mm OD
71338663	R3™ Multi Hole Acetabular Shell 48mm OD
71338664	R3™ Multi Hole Acetabular Shell 50mm OD
71338665	R3™ Multi Hole Acetabular Shell 52mm OD
71338666	R3™ Multi Hole Acetabular Shell 54mm OD
71338667	R3™ Multi Hole Acetabular Shell 56mm OD
71338668	R3™ Multi Hole Acetabular Shell 58mm OD
71338669	R3™ Multi Hole Acetabular Shell 60mm OD
71338671	R3™ Multi Hole Acetabular Shell 62mm OD
71338672	R3™ Multi Hole Acetabular Shell 64mm OD
71338673	R3™ Multi Hole Acetabular Shell 66mm OD
71338674	R3™ Multi Hole Acetabular Shell 68mm OD
71338675	R3™ Multi Hole Acetabular Shell 70mm OD
71338676	R3™ Multi Hole Acetabular Shell 72mm OD
71338677	R3™ Multi Hole Acetabular Shell 74mm OD

*Variants of R3™ non-HA Acetabular Shells that are commercially available vary per region. Only commercially available R3™ non-HA Acetabular Shells can be used in the study.

Table 24-4: OXINIUM Femoral Heads

Catalog Item #	Catalog Item Description
71342200	12/14 Taper Femoral Head 22mm O.D. +0
71342204	12/14 Taper Femoral Head 22mm O.D. +4
71342208	12/14 Taper Femoral Head 22mm O.D. +8
71342803	12/14 Taper Femoral Head 28mm O.D. -3
71342800	12/14 Taper Femoral Head 28mm O.D. +0
71342804	12/14 Taper Femoral Head 28mm O.D. +4
71342808	12/14 Taper Femoral Head 28mm O.D. +8

Table 24-5: List of Compatible Stems

Product Name
SMF™ Hip Stem
Synergy™ Hip Stem
Anthology™ Hip Stem
Spectron™ Hip Stem **(not for this clinical trial)*
POLARSTEM™
SL-PLUS™ Hip Stem
SLR-PLUS™ Hip Stem **(not for this clinical trial)*
SL-PLUS™ (S-Version) Hip Stem
SL-PLUS MIA™ Stem
SLR-PLUS™ (S-Version) Hip Stem **(not for this clinical trial)*
POLARSTEM™ collared and noncollared (Standard and Lateral) and Valgus Femoral Stem with Ti/Ha **(not for this clinical trial)*
Anthology™ AFIT Hip Stem **(not for this clinical trial)*
ECHELON™ Hip Stem **(not for this clinical trial)*
REDAPT Hip Stem **(not for this clinical trial)*

24.4 HEALTH ECONOMIC OUTCOME MEASURES/QUALITY OF LIFE MEASURES

For more information on EQ-5D-5L and HOOS JR scores, please refer to the eCRF table.

24.5 PRINCIPAL INVESTIGATOR OBLIGATION

24.5.1 Responsibilities of Clinical Trial Institutions and Investigators (Decree No. 25)

Article 59 Before accepting clinical trial, clinical trial institutions shall evaluate relevant resources in accordance with the characteristics of investigational medical devices to decide whether to accept this clinical trial.

Article 60 Clinical trial institutions shall properly keep clinical trial records and basic documents according to the agreement with the sponsor.

Article 61 Investigators who are in charge of the clinical trial shall:

(I) Have professional title and qualification above associate level, such as associate chief physician, associate professor and associate researcher in the clinical trial institutions;
(II) Have professional knowledge and experience required for investigational medical devices and pass relevant trainings if necessary;
(III) Be familiar with clinical trial requirements provided by sponsor, and the data and literatures related to clinical trial;
(IV) Be able to coordinate, allocate and assign personnel and devices of this trial, and to handle the adverse events and other correlating events related to investigational medical devices;
(V) Be familiar with relevant national laws, regulations and this Provision.

Article 62 Prior to a clinical trial, the medical device clinical trial administrative department of clinical trial institutions shall coordinate sponsor to file applications to the ethics committee and submit relevant documents in accordance with relevant provisions.

Article 63 Investigators shall ensure that the staff member participating in the trial are familiar with the principles, indications, product performance, operating methods, installation requirements and technical specifications of investigational medical devices, understand preclinical research data and safety data of investigational medical devices, and master precautions and emergency treatment for possible risks in clinical trial.

Article 64 Investigators shall ensure all participants of clinical trial fully understand the clinical trial protocol, relevant provisions, characteristics of investigational medical devices and relevant responsibilities of clinical trial, make sure that enough subjects meeting inclusion criteria in clinical trial protocol can be enrolled into clinical trial, ensure enough time in the agreed trial period, to implement and complete clinical trial safely according relevant regulations.

Article 65 The investigator shall ensure that the investigational medical devices are only used for subjects of the clinical trial, and used for free.

Article 66 Investigators shall strictly comply with clinical trial protocol. Without consent of sponsor and ethics committee or approval of China Food and Drug Administration in accordance with regulations, investigators shall not deviate the protocol or substantially change the protocol. However, in case of an emergency that subjects face direct danger that needs to be eliminated immediately, it can be reported in writing afterwards.

Article 67 Investigators shall be responsible for recruiting subjects and talking with subjects or their guardians. Investigators are responsible to specify the details relating to investigational medical devices and clinical trial for subjects, inform subjects of possible benefits and known and foreseeable risks, and obtain the signed and dated informed consent form from subjects and their guardians.

Article 68 Investigators and other personnel participated in the trial shall not force or induce subjects in improper way to take part in the trial.

Article 69 In case of finding unanticipated adverse events of investigational medical devices during clinical trial, investigators shall revise relevant content of informed consent form together with the sponsor. After being reviewed and approved by ethics committee in accordance with relevant working procedure, the affected subjects and their guardians shall resign the revised informed consent form for confirmation.

Article 70 Investigators shall be responsible for making decisions relating to clinical trial. In case of adverse events relating to clinical trial, clinical trial institutions and investigators shall provide sufficient and timely treatment and management to subjects. In case subjects have complications and need treatment and management, investigators shall timely notify subjects.

Article 71 In case of serious adverse events during clinical trial, investigators shall take proper treatment measures for subjects immediately, then report to medical device clinical trial administrative departments of clinical trial institutions where they belong to, and notify sponsor in writing through them. Clinical trial administrative departments of medical devices shall report to corresponding ethics committee and Food and Drug Administration of province, autonomous region or municipality and the Health and Family Planning Commission where the clinical trial institution is located in written form within 24 hours. For lethal events, clinical trial institutions and investigators shall provide all necessary data to ethics committee and sponsor.

Article 72 Investigators shall record all adverse events and device deficiency that occur during the process of clinical trial, analyze event cases together with sponsor, draft written analysis report, put forward opinions of continuing, suspending or terminating the trial, and report to ethics committee for review through medical device clinical trial administrative departments of clinical trial institutions.

Article 73 Investigators shall ensure that clinical trial data are filled in case report forms accurately, completely, clearly and timely. Case report forms shall be signed by investigators. Any change of data shall be signed and dated by investigator, original records should be kept, clear and recognizable.

Article 74 Clinical trial institutions and investigators shall ensure authenticity, accuracy, clarity and safety of data and documents generated in clinical trial.

Article 75 Clinical trial institutions and investigators shall accept the monitoring and audit of sponsor as well as supervision of ethics committee, and provide all required records relating to the trial. In case Food and Drug Administration and Health and Family Planning Commission send inspectors to implement inspection, clinical trial institutions and investigators shall cooperate with them.

Article 76 In case clinical trial institutions and investigators identify risks overweighting possible benefits, or have obtained the results that is sufficient to judge the safety and efficacy of investigational medical devices, thus need to suspend or terminate clinical trial, it is required to notify subjects and ensure subjects to obtain proper treatment and follow-up, report in accordance with regulations and provide detailed written explanation at the same time. If necessary, report to the Food and Drug Administration of province, autonomous region or

municipality where it locates. In case of receiving the notification of sponsor or ethics committee on the need of suspending or terminating clinical trial, investigators shall timely notify subjects and ensure subjects to obtain proper treatment and follow-up.

Article 77 In case the sponsor violates relevant regulations or request to change the trial data and conclusion, clinical trial institutions and investigators shall report to Food and Drug Administration of province, autonomous region or municipality where the sponsor is located or report to the China Food and Drug Administration.

Article 78 At the end of a clinical trial, the investigator shall ensure the completion of all records and reports. Meanwhile, the investigator shall ensure the quantity of received investigational medical devices is consistent with the used, discarded or returned devices, and ensure that the rest investigational medical devices are disposed properly and recorded for filing.

Article 79 Investigators can authorize corresponding personnel to recruit subjects, continuously communicate with subjects, record the clinical trial data, and manage investigational medical devices in accordance with the needs of clinical trial. Investigators shall implement relevant training for the authorized personnel and document accordingly.

24.5.2 Principal Investigator Obligations (ISO14155:2011)

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.
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 one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.
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 14155:2011.
        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 his/her 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 his/her 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 his/her 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 as his/her medical condition allows.

d. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or his/her 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. 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

iii. A statement declaring that discontinuation 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

vi. A statement confirming that the subject or his/her 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 his/her 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 his/her 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,

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. allow and support the Sponsor to perform monitoring and auditing activities,

m. be accessible to the monitor and respond to questions during monitoring visits,

n. allow and support regulatory authorities and the IEC when performing auditing activities,

o. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and 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. 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 supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.