A Safety Follow Up Study in Australian Subjects implanted with the SMF Short Modular Femoral Stem Hip System

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Study Product Name:	SMF Short Modular Femoral Stem
Sponsor:	Smith & Nephew Surgical Pty Limited 85 Waterloo Road North Ryde NSW 2113 Australia

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Abbreviations and Definitions:

AE	Adverse Event
ADE	Adverse Device Effect
CAPA	Corrective and Preventive Action
CoCr	Cobalt Chrome
CRO	Contract Research Organization
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
EC	Ethics Committee
EOS	End of Study
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification Number
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
MARS MRI	Metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI)
PI	Principal Investigator
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SMF	Short Modular Femoral
SOP	Standard Operating Procedure
THA	Total Hip Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect

Protocol Synopsis:

Study Title	A Safety Follow Up Study in Australian Subjects implanted with the SMF Short Modular Femoral Stem Hip System
Short Title	SMF modular stem safety follow up study
Sponsor	Smith & Nephew Surgical Pty Ltd 85 Waterloo Road North Ryde NSW 2113
Study Type	Post Market Study
Study Device	SMF Short Modular Femoral Stem
Indications	Total Hip Arthroplasty
Study design	A single center, single arm, consecutive series study
Study Objective	The primary objective of this study is to provide safety data for the SMF Short Modular Femoral Stem Hip System up to a follow up period of 20 years post implantation
Primary Endpoint	Safety Data based on the following assessments: ▪ Whole blood cobalt and chromium ion levels collected annually for symptomatic subjects and every 3 years for non-symptomatic subjects ▪ Metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) or Computed Tomography (CT) in subjects with whole blood cobalt and/or chromium > 7 parts per billion (ppb)
Secondary Endpoints	▪ Standard of Care Radiographic assessments ▪ HOOS JR Hip Questionnaire ▪ Revision of any component of the study device for any reason ▪ Adverse events assessment
Length of Study	Approximately Twelve Years. Subjects have been implanted with the SMF Device in 2009 and 2010 at the investigational site. The Baseline visit will be determined as the first visit to site after Ethics approval for the study has been received. This will be approximately 8-9 years post implant. Enrolled subjects will be followed up to 20 years post SMF implant
Number of Sites	1 site (Australia)
Sample Size	Up to 26 subjects based on feasibility only
Inclusion Criteria	▪ Subject has undergone primary total hip arthroplasty with the SMF Short modular femoral stem at the study site and still has the original implant at the time of Ethics Committee (EC) approval of the study ▪ Subject is willing and able to participate in follow-up visits at the study site

Exclusion Criteria	▪ The Subject, in the opinion of the PI, has an emotional or neurological condition that would affect their ability or willingness to participate in the study including mental illness, mental retardation, drug or alcohol abuse ▪ Subject is known to be at risk for lost to follow-up or failure to return for scheduled visits

1.0 Background and Study Rationale

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; ISO 14155:2011 Clinical investigation of medical devices – Good Clinical Practice; ICH-E6 and the approving Ethics Committee Guidelines.

In compliance with post-marketing surveillance obligations, Smith & Nephew continually monitors the performance of its products. During a recent review of product complaints received by Smith & Nephew and clinical study data associated with the modular hip prostheses, the Sponsor observed a rate of complaints higher than comparable monolithic hip prostheses. Based on an analysis of available data sets, Smith & Nephew considers that patients implanted with the modular neck hip prostheses may be at greater risk of revision surgery than with comparable monolithic products. For this reason, on a precautionary basis Smith & Nephew issued a voluntary field safety corrective action for the modular neck hip prostheses. With this voluntary market removal of the modular neck, SMF modular stems were removed from the market in November 16, 2016.

The purpose of the current investigation is to provide safety data for the SMF Short Modular Femoral Stem Hip System in implanted subjects. The safety data will be based on assessments of whole blood cobalt and chromium ion levels and Metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) or Computed Tomography (CT) in subjects with cobalt and/or chromium > 7parts per billion (ppb).

2.0 Study Objectives

The primary purpose of this study is to provide safety data on the SMF Short Modular Femoral Stem THA system with regards to laboratory, radiographic and clinical outcomes in implanted patients.

3.0 Study Design

This is a single arm, consecutive series study to collect relevant clinical, laboratory and radiological data in up to 26 subjects, who have been implanted with the SMF Short Modular Femoral Stem THA system at 1 site in Australia.

The Baseline visit will be determined as the first visit to site after Ethics approval for the study has been received. This will be approximately 8-9 years post implant. Enrolled subjects will be followed up to 20 years post SMF implant. The Baseline visit assessments are described in Section 5.5 and 5.6. Post Baseline, the study will allow for metal ion assessments every 3 years for asymptomatic subjects and annual assessments for subjects with pain, swelling, and/or functional limitations if assessed by the Principal Investigator to be related to the SMF implant, having ruled out all other probable causes for the subject. If the subject has elevated whole blood cobalt or chromium (defined as >7ppb) a MARS MRI or CT will be obtained. These types of imaging techniques are aimed at

detecting inflammatory degenerative evolution of periarticular soft tissues including pseudo-tumors. A functional Questionnaire, HOOS JR Questionnaire will be completed at all patient site visits.

3.1 Primary Endpoint

- Safety assessment of the SMF Short Modular Femoral Stem implanted Subjects using Metal Ion Analysis and MARS MRI/ or CT at Baseline and at protocol scheduled visits at the 1 yearly or at the 3 yearly time point as per the study schematic Table 1.

  Metal Ion Level assessment
  - All Subjects at Baseline and every three years afterwards will have whole blood collected for metal ion testing of whole blood cobalt and chromium
  - Symptomatic subjects with pain, swelling, and/or functional limitations if assessed by the PI to be related to the implant will have whole blood collected for metal ion testing of cobalt and chromium annually

  MARS MRI/CT
  - Subjects with whole blood cobalt and/or chromium > 7 ppb will have MARS MRI (or CT if MRI is contraindicated) performed

3.2 Secondary Endpoints

- Revision of any component for any reason
- Standard of Care Radiographic assessments
  - Loosening as indicated by radiolucencies > 2mm
  - Evidence of surface wear or particulate debris generation as indicated by early osteolysis, implant migration, or other clinical or radiographic abnormalities such as pseudo tumors or corrosion
- HOOS JR Questionnaire
  - The score will be calculated to assess clinical efficacy
- Adverse Events assessment
  - Safety will be evaluated by assessing the frequency and nature of adverse events as defined in the Safety Reporting section

4.0 Study Device

4.1 Device Description

The study device in this study is a SMF Short Modular Femoral Stem.

The **SMF Short Modular Femoral Stem** is described below:

A. Femoral Hip Stem

The femoral stem is a straight, tapered and proximally loading stem designed to match the geometry of the femur. The stems are proportionally sized and shaped in sizes 1 through 9. The stem is made of coated titanium alloy and is matched with a polished modular neck. Each femoral stem is proximally coated with Smith & Nephew's StikTite porous coating.

B. Modular Neck

The short mini stem mates with a modular neck designed with various offsets. The modular neck is manufactured from polished Cobalt Chrome. All modular necks have a 12/14 taper and are compatible with various heads.

4.2 Device Accountability

As this is a post-surgical safety data collection study, no device accountability will be performed. Device revisions and device complaints will be followed up as per Sponsor guidelines. Every effort will be made to return devices if applicable and to follow up all device complaints according to device safety processes and Sponsor guidelines.

5.0 Study Population

5.1 Screening and Enrollment

Subjects will be screened according to the study inclusion and exclusion criteria. Subjects meeting the eligibility criteria will be contacted by the PI and be invited to participate in the study.

All potential subjects who undergo the screening process and are excluded from the study will have the reason for exclusion documented on a Screening and Enrollment Log. The reasons for exclusion may include refusal to participate in the study visits, lost to follow-up or that the subject is deceased.

Subjects will be assigned consecutive Subject Identification (ID) numbers, by date of PI contact to discuss study participation.

5.2 Informed Consent

The study will be explained to the eligible subject by the PI and if the subject agrees to participate, the informed consent process will be conducted. The subject will be given time to discuss study participation and ask questions. The informed consent form must be signed before any study related procedure is performed.

The informed consent process will be documented in the subject's medical record and in the study Case Report Forms (CRFs). The informed consent form (ICF) will be placed in the subject file and a copy will be provided to the subject.

5.3 Subject Inclusion Criteria

Subjects must meet the following inclusion criteria:

- The Subject has undergone primary total hip arthroplasty with the SMF Short modular femoral stem at the study site and still has the original implant at the time of Ethics Committee (EC) approval of the study
- Subject is willing and able to participate in follow-up visits at the study site

5.4 Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria will be excluded from study participation:

- Subject, in the opinion of the PI, has an emotional or neurological condition that would affect their ability or willingness to participate in the study including mental illness, mental retardation, drug or alcohol abuse
- Subject is known to be at risk for lost to follow-up, or failure to return for scheduled visits

5.5 Data Collection

All subjects will have a Baseline data collection and at the yearly or 3 yearly visits as described below and in the study schematic Table 1. Data will also be collected at unscheduled visits which will be conducted if the subject experiences a device related adverse event in between scheduled visits.

5.5.1 Baseline Visit

- Informed Consent
- Implant and Joint Status
- Operative Date
- Demographics
- Medical History and Concomitant Medication
- HOOS JR Questionnaire
- Radiographic evaluation
- Adverse events assessment
- Metal Ion Level assessment
    - Whole blood will be collected for metal ion testing of cobalt and chromium
- MARS MRI/CT
    - Subjects with whole blood metal ion levels > 7 ppb will have a MARS MRI performed (or CT if the MRI is contraindicated)
- Study termination, if applicable

5.5.2 1 Year/3 Year Visits (± 3M) up to 20 years post implant Follow Up

Annual visit schedule for symptomatic subjects and 3 Year visit schedule for non-symptomatic subjects

- Implant Status

- Demographics
- Medical History and Concomitant Medication
- HOOS JR Questionnaire
- Radiographic evaluation
- Adverse events assessment
- Metal Ion Level assessment
    - Whole blood will be collected for metal ion testing of cobalt and chromium
- MARS MRI/CT
    - Subjects with metal ion levels > 7 ppb will have a MARS MRI performed (or CT if MRI is contraindicated)
- Study termination, if applicable

5.5.3 Unscheduled Follow-up Visit

The unscheduled study visit will be determined by the PI for safety follow up. The visit assessments will be as required for safety follow up of the individual subject.

5.6 Table 1: Study Schematic

The intervals and schedule of events for this study are provided in Table 1.

Schedule of events	Screening/ Telephone Call	Baseline Visit	1 Year visit for symptomatic subjects/3 Year visit for non-symptomatic subjects (± 3M)	EOS Visit (20 years post SMF Implant procedure) (± 6M)	Unscheduled visit
Subject Status verification	X[1]				
Informed Consent		X			
Inclusion/Exclusion Criteria		X			
Implant Status	X[1]	X	X	X	X
Operative Date		X			
Demographics		X			

Schedule of events	Screening/ Telephone Call	Baseline Visit	1 Year visit for symptomatic subjects/3 Year visit for non-symptomatic subjects (± 3M)	EOS Visit (20 years post SMF Implant procedure) (± 6M)	Unscheduled visit
Medical History and Concomitant Medication		X	X	X	X
HOOS JR Questionnaire		X	X	X	X
X-ray Assessments		X[2]	X[2]	X[2]	X[3]
Adverse Events Assessment		X	X	X	X[3]
Metal Ion level Assessments		X	X	X	X[3]
MARS MRI /CT		X[3]	X[3]	X[3]	X[3]
End of Study		X[3]	X[3]	X	X[3]

X[1] Verification of Eligibility via telephone contact to determine patient and implant status
X[2] X Ray Assessments/Radiographs will be in line with standard of care
X[3] If Applicable
HOOS JR: The Hip Osteoarthritis Outcomes Score Junior is a validated short questionnaire that the patient completes focusing on joint pain, stiffness, and function relating to daily living.

6.0 Subject Completion and Discontinuation

6.1 Conditions for Subject Termination

All reasonable efforts should be made to retain all consented subjects out to the 20 year post-implant study duration. There are multiple reasons a subject may terminate participation from the study. For each case, the reason will be documented on the Study Termination CRF detailing the circumstances leading to the withdrawal.

6.1.1 Screen Failure

- Subjects known to have received the SMF Short Modular Femoral stem as a total hip arthroplasty who does not agree to the prospective on-site study visits
- A Subject who has undergone a SMF Short Modular Femoral Stem THA but does not meet all inclusion/exclusion criteria and therefore is not enrolled in the study
- A Subject is not enrolled by the Investigator for any reason
- Subject does not give consent to provide any information for the purposes of the study when approached for participation

The reasons for the screen failure subjects will be recorded in the Site's Screening and Enrollment Log.

6.1.2 Voluntary Withdrawal

Study participation is voluntary and subjects may withdraw their participation from the study without giving reason for doing so. The withdrawal will be documented in the subject's CRF.

6.1.3 Lost to Follow-Up

Study personnel must make a reasonable effort to contact the subject and document the contact attempts according to the site's policies prior to declaring a subject to be lost to follow-up. Copies of all attempts to reach the subjects per regular mail, email and/or any other means should be documented in the subject's medical record and the CRF.

6.1.4 Study Termination by Investigator/Sponsor

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

- subject noncompliance to study visit schedule
- subject lost to follow-up
- Investigator or the Sponsor terminates the study for any reason

6.1.5 Pregnancy

In the unlikely event that a subject becomes pregnant from the time point of signing the Informed Consent until the end of the study, study procedures that are contraindicated during pregnancy and/or lactation (e.g. x-rays) will not be obtained. However, the subject will continue to be followed and information will be collected regarding the outcome of the birth.

6.1.6 Study Site Discontinuation

Study site participation may be discontinued if the Sponsor, the Investigator or the approving Ethics Committee of the study site determines it necessary for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and GCP.

6.1.7 Revisions

Subjects who have undergone a revision THA procedure to the primary SMF Short Modular Femoral stem, following the initial surgery, will be considered discontinued from the date of the revision procedure and will not receive any further study-related follow-up from this date. The End of Study CRF and Serious Device Adverse Event (SDAE) case report form will be completed to document the date of revision, adverse events and any radiographic assessment if available.

6.1.8 Study Discontinuation by Sponsor

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

If the study has been discontinued for safety reasons, the Sponsor will advise the Investigator on the proper procedure to ensure the safety of enrolled subjects is maintained.

For each case, information will be documented on the Study Termination Form, detailing circumstances leading to the discontinuation.

7.0 Safety Reporting

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether or not related to the investigational medical device. All adverse events and device deficiencies noted by study staff or reported by the subject occurring from the time of signing the informed consent through to study completion must be recorded on the appropriate CRFs and reported as below. This includes worsening of any conditions previously recorded as part of the medical history assessment.

Adverse Device Effects occurring after study completion will be handled as product complaints reportable by the Sponsor and will not be entered into the study database.

7.1 Definitions for Safety Reporting

7.1.1 Adverse Event (AE)

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

7.1.2 Adverse Device Effect (ADE)

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

This definition includes:

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

7.1.3 Serious Adverse Device Effect (SADE)

An SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.4 Serious Adverse Event (SAE)

An SAE is an adverse event that:

- led to death
- led to serious deterioration in the health of the subject, that either resulted in:

1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

- led to fetal distress, fetal death or a congenital abnormality or birth defect

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

7.1.5 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which, by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or the clinical investigation plan.

7.1.6 Device Deficiency

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

For the purpose of this study, device deficiencies should be reported when they concern any component of the study device.

7.1.7 Revisions

All events that lead to revisions will be collected as an SADE.

7.2 Safety: Investigator's Responsibilities

The Investigator shall record required safety events and observed device deficiencies, together with an assessment, in the subject's source data and the appropriate CRF and submit them to the Sponsor according to the timelines described below.

At each contact with the subject, the Investigator must seek information on AEs by specific questioning and, as appropriate, by assessment of the subject. These AEs must be recorded in Standard English medical terminology. AEs should be followed by the Investigator until the events are resolved, the subject is lost to follow-up or through to the end of the study, whichever timing occurs first. Unresolved AEs at the end of the subject's participation will be monitored by the Investigator as part of the site's normal standard of care.

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

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

The Investigator is responsible for describing the relationship of the AE to the study device/procedure based on the following definitions:

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

7.3 Timelines for Submission of Safety Information

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

The Investigator will report to the Sponsor:

- As soon as possible, but **no greater than 24 hours upon becoming aware of the SAEs, SADEs, USADEs and device deficiencies that could have led to a SADE.**
- **Revisions: within 24 hours upon becoming aware of the event.** The Sponsor will provide an explant retrieval kit on becoming aware of a revision and ask the Investigator to return any revised components for retrieval analysis, if possible.

Upon request, the Investigator may also be asked to supply the Sponsor with any additional information related to the safety reporting of a particular event.

The Principal Investigator will be responsible for reporting SAEs, SADEs, USADEs, and device deficiencies that could have led to a SADE, as required by the IRB/EC.

7.4 Safety Reporting: Sponsor's Responsibilities

The Sponsor will provide progress reports on safety events to the Investigator to report to the Ethics Committee as required.

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

8.0 Statistical Procedures

This is a single center, single arm, consecutive series study to evaluate the safety outcomes of hip arthroplasty with the SMF Short Modular Femoral Stem THA system. Up to 26 subjects will be enrolled in the study. The sample size was chosen based on the feasibility of recruitment only without regard for statistical power as this is a descriptive study and there is no available previous data for sample size justification.

8.1 Analysis Population

Intent-to-Treat (ITT) Population

The ITT population includes all subjects who met the inclusion criteria and are sequentially enrolled to the study based on medical record review and confirmation of Short Modular Femoral Stem implant surgery for a THA arthroplasty prior to IRB/EC approval of this protocol.

Per Protocol (PP) Population

The Per-protocol population (PP) population includes all enrolled subjects who received the assigned treatment and do not have major protocol violations. The PP population will be established after a review of protocol deviations. All efficacy analyses will be performed on the PP population.

8.2 Statistical Design

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The following is a brief description of the analyses to be described in this plan. The SAP will be more detailed and account for all analyses.

8.2.1 General

The subjects will be described and summarised using the collected baseline demographic and medical variables which include but are not limited to age, gender, ethnicity, medical and medication history, diagnostic factors.

Primary and secondary endpoints will be evaluated using listings and appropriate summary statistics. The summary statistics for both primary and secondary outcomes will be reported together with a 95% confidence interval to assess the degree of precision in the estimates.

Summary statistics for baseline data, primary and secondary endpoints will be given according to the nature of the variable, continuous or categorical. For categorical variables, the number of observations, mean, standard deviation, median, minimum, and maximum will be presented, while for categorical variables the number of observations, frequency, and percentages will be reported.

All statistical tests will be exploratory in nature as the study is not powered for any statistical testing. Appropriate parametric and/or non-parametric analyses will be chosen for statistical analysis. Test of association for the table of counts will be based on the Fisher's Exact Test unless otherwise inappropriate. The exploratory analysis of continuous variables will be done using t-test if appropriate. The Wilcoxon rank-sum test will be explored if the data is non-normal. All statistical tests will be considered at 5% significance level.

All statistical analyses and calculation of confidence intervals will be performed using SAS software.

8.3 Efficacy Analysis

The primary objective of this study is to provide safety data for the SMF Short Modular Femoral Stem Hip System up to a follow up period of 20 years post implant. The indicators of efficacy of hip arthroplasty with the SMF Short modular femoral stem will be evaluated through the analysis of primary and secondary endpoints. For all continuous endpoints, 95% confidence intervals (CI) for the means will be reported.

8.3.1 Analysis of Primary Endpoint

- Safety assessment of the SMF Short Modular Femoral Stem implanted Subjects using Metal Ion Analysis and MARS MRI/ or CT at Baseline and at protocol scheduled visits at the 1 yearly or at the 3 yearly time point as per the study schematic Table 1.

  Metal Ion Level assessment
  - All Subjects at Baseline and every three years afterwards will have whole blood collected for metal ion testing of whole blood cobalt and chromium
  - Symptomatic subjects with pain, swelling, and/or functional limitations if assessed by the PI to be related to the implant will have whole blood collected for metal ion testing of cobalt and chromium annually

  The concentration levels of cobalt and chromium will be summarized using mean, median, SD, minimum and maximum at all recorded time points for all subjects. The results will be further categorized as subjects with pain, swelling and functional limitations. An exploratory ANOVA model will be fitted to evaluate any variation in changes over time.

MARS MRI/CT

- Subjects with whole blood cobalt and/or chromium > 7 ppb will have MARS MRI (or CT if MRI is contraindicated) performed

Based on the MARS MRI/CT results, a binary variable will be used to categorize subjects with blood cobalt and/or chromium > 7 ppb or below at all recorded time points. The frequencies together with percentages will be reported. The results will be further categorized as subjects with pain, swelling and functional limitations.

8.3.2 Analysis of Secondary Endpoints

- Revision of any component for any reason – Revision will be evaluated as the frequency of subjects with component revision at the end of study and expressed as a percentage of the full analysis set.
- Standard of Care Radiographic assessments
    - Loosening as indicated by radiolucencies > 2mm - a binary variable will be used to categorize subjects with radiolucencies > 2mm or below at all recorded time points. The frequencies together with percentages will be reported. The results will be further categorized as subjects with pain, swelling and functional limitations.
    - Evidence of surface wear or particulate debris generation as indicated by early osteolysis, implant migration, or other clinical or radiographic abnormalities such as pseudo tumors or corrosion

The presence of surface wear and all types radiographic abnormalities will be summarized as frequencies together with percentages at all recorded time points.

- HOOS JR Questionnaire
    - The score will be calculated to assess clinical efficacy

The HOOS score will be summarized using mean, median, SD, minimum and maximum at all recorded time points for all subjects. The results will be further categorized as subjects with pain, swelling and functional limitations. An exploratory t-test will be fitted to evaluate the difference between baseline and end of study scores.

- Device Related Adverse Events
    - Safety will be evaluated by assessing the frequency and nature of Device related adverse events as defined in the Safety Reporting section

8.3.3 Analysis of Safety Endpoints

All adverse events will be tabulated and categorized as follows: adverse device effect, serious adverse device effect, serious adverse event, unanticipated Serious Adverse Device Effect and device deficiency. Frequencies together with percentages will be given.

8.4 Hypothesis and Sample Size Calculation

The sample size was chosen based on the feasibility of recruitment only without regard for statistical power as this is a descriptive study to establish efficacy and safety data based on the selected primary outcomes. There is no available previous data or data from similar studies for sample size justification.

8.5 Missing Data

A complete accountability report, along with the explanation for lost-to-follow-up, death, revision, and withdrawn subjects, will be provided in the Clinical Study Report (CSR). A complete list of the informative/non-informative missing data will be also be provided in the CSR. Due to the nature of the study, no imputation of missing data is planned.

9.0 Ethical Considerations

9.1 Ethical Approval

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

9.2 Protocol Amendments

Neither the Investigator nor the Sponsor will modify this protocol without mutual agreement. After agreement to initiate the modification, in the form of a protocol amendment, the Investigator will agree not to implement this modification until instructed to do so by the Sponsor. It will be necessary to obtain Ethics Committee approval prior to implementation of any change in the protocol that may affect the scientific soundness or the rights, safety, or welfare of the subjects involved. Notification shall be submitted to the IRB/EC of the study site by the Investigator.

9.3 Informed Consent

All study subjects must sign an IRB/EC approved ICF according to ISO14155 guidelines, GCP guidelines and all applicable national regulations. The subjects must be informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written consent form. The subject shall have sufficient opportunity to consider participation in the study; a subject cannot be led to believe that they are waiving their rights as a subject or the liability of the Sponsor or Investigator. The Investigator will retain the original copy of the signed consent form in the study files. A copy shall be provided to the subject.

The Investigator must apply for the appropriate IRB/EC approvals on this study.

10.0 Risk – Benefit Analysis

10.1 Study Related Risks

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

- **X-Ray Exposure:** This study involves the use of x-ray evaluation. X-ray exposure is cumulative over a lifetime and total exposure should be kept to a minimum. However, if the x-ray exposure when participating in the study is equivalent to the exposure the subject would receive if they chose not to participate in the study, there is no additional risk associated with this study.
- **Loss of Confidentiality:** As a result of participating in the study there could be a risk of loss of protected subject information confidentiality. All applicable confidentiality standards and data protection and privacy laws will be followed by the Sponsor, Smith & Nephew, to ensure that data collection is handled in confidence. Data will be coded and handled only by appropriately qualified and authorized personnel.
- **Phlebotomy:** Blood draws will be required to obtain blood for metal ion assessment of cobalt chrome and chromium levels. Pain and bruising and possible infection at the site of blood draw and fainting may occur. The risk for these events will be reduced by use of approved medical equipment for blood draws and personnel trained in phlebotomy.
- **Metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI)/Computerized tomography (CT)**: MARS MRI will be indicated for study subjects who are symptomatic according to the Protocol. Radiologic evaluations used in this study are to be considered standard of care. There is no additional study-related radiologic exposure. The monitoring of symptomatic study subjects with MARS MRI or CT (where MRI is not recommended) will follow standard of care recommendations.

10.2 Study Related Benefits

The information gained from this study may help improve the assessment and treatment of people that have undergone implantation with the SMF Short Modular Femoral Stem THA system.

11.0 Monitoring Procedures

11.1 Source Documentation

The Investigator will be responsible for obtaining and maintaining complete subject health information in the medical record for each subject (source documents). Examples of source documents are: hospital records, clinic and office charts, memoranda, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection reports and shipment records, and research subject files.

CRFs may be used as source documents if they represent data being collected for the sole purpose of the study and are the location that data is initially recorded.

As a minimum entry in the medical records, the Principal Investigator shall ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical study and if they completed the study per protocol or discontinued early and the reason for discontinuation.

11.2 Direct Access

This study will be monitored by the Sponsor or a qualified person designated by the Sponsor. This qualified person may be an employee of the Sponsor or of a Contract Research Organization (CRO; Sponsor's agent).

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

11.3 Site Qualification Visit

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

11.4 Activities Prior to Study Initiation

The Investigator must ensure the activities below are completed prior to the initiation of the study and provide supporting documentation to the Sponsor:

- **Clinical Trial Agreement (CTA)**: must be fully executed with the site and the Sponsor and any other appropriate party.
- **Documentation of Qualifications:** a current, signed and dated Curriculum Vitae (CV) for Investigator and for all key members of the Investigator study site team listed on the Delegation of Authority Log must be submitted to the Sponsor prior to the study and updated as applicable to staff changes and confirmed at close out visit.
- **Conflict of Interest:** The participating Investigator is required by ISO 14155 to provide details of conflict of interest (including financial, if applicable) according to local regulations. This information must be updated by the Investigator and submitted to the Sponsor if any changes occur through the duration of the study.

11.5 Site Initiation Visit

A site initiation visit will be performed by the Sponsor following execution of the Clinical Trial Agreement and documented HREC approval to provide training to the site on the specifics of the study and its conduct. The site must have written approval from the Sponsor before beginning subject enrolment.

11.6 Interim Monitoring Visits

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

- verify informed consent process
- perform source data verification
- verify that source documentation is complete and available
- ensure compliance with the protocol
- ensure all required study documentation is complete and available in the Investigator Master Site File

11.7 Sponsor Audits and Regulatory Inspection

The study conduct at site may be evaluated by Quality Assurance auditors, who may be an employee of the Sponsor or its designee. These parties must have access to all study reports and source documentation, regardless of location and format.

11.8 Closeout Visit

A study close out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements regarding records retention and IRB/EC reporting requirements.

11.9 Documentation of Monitoring Visits

Activities associated with a monitoring visit will be documented by the monitor.
These will include:

- Signing the on-site monitor visit log
- Providing a follow up letter to the Investigator following each monitor visit summarizing the visit and detailing any site deficiencies and action items requiring reconciliation

12.0 Data Handling and Record Keeping Requirements

CRFs will be supplied by the Sponsor. Subjects will be identified by a Study ID number and subject identification code. Only the Investigator site will have the key to identify individual subjects. The Investigator will be responsible for the timely and accurate completion of CRFs. Data collected for the purposes of this protocol are to be recorded on the CRFs at the time of the scheduled visits. Completed CRFs should be sent to the Sponsor, either by fax or by e-mail, as soon as possible.

All documents related to the study must be securely archived at the study site or in an archiving facility.

12.1 Data Recording and Record Retention

Clinical research records shall be stored in a manner that ensures privacy, confidentiality, security and accessibility of the records both during and after the conduct of the study. The Investigator/Institution will take measures to

prevent accidental or premature destruction of those documents. The Investigator must retain essential study documents for at least 2 years after the latest of the following: The date the study is terminated, completed, or the date the documents are no longer needed to support a premarket approval application. If the Investigator needs to dispose of the documents, the Sponsor should be contacted for approval prior to disposal or destruction. For discontinued product, the essential documents will be retained until at least 2 years have elapsed since the formal discontinuation (via notification of the FDA or other regulatory agency) of clinical development of the investigational product. The investigator will retain these documents for a longer period if required by the applicable local laws. If the responsible Investigator retires, relocates, or withdraws from responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

13.0 Deviations from Protocol

A protocol deviation is an instance of failure, intentionally or unintentionally, to follow the requirements of the protocol. Protocol deviations include but are not limited to: deviations from inclusion/exclusion criteria, missed or otherwise inadequate data collection, study visits outside the window, and violation of GCP guidelines.

13.1 Protocol Deviation Reporting Requirements

Deviations must be reported to the Sponsor through the Protocol Deviation Log as soon as reasonably possible.
When protocol deviations affect the scientific soundness of the study, or the rights, safety or welfare of the study subjects, the Investigator must report protocol deviations to the IRB/EC of the study. The local IRB/EC should be consulted on protocol deviation reporting requirements.

Investigators and all study staff (site staff and Sponsor staff) are responsible for ensuring adherence to the study protocol. During the monitoring visits, the Sponsor representative will review all deviations with the Investigator. If a deviation is discovered outside of a monitoring visit, it should be evaluated via phone, email or letter. Appropriate measures to address the occurrence, additional monitoring visits, or audit of the study should be taken, which may include defining and implementing a Corrective and Preventive Action (CAPA).

14.0 Publication Policy

14.1 Investigator Publication

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

No patent application(s) based on the results of the study may be made by the Investigator nor may assistance be given to any third party to make such an application without the written authorization of Sponsor. The publication of results in the academic journals will be guided by the Site Agreements between the Sponsor and the Investigator.

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