Intraoperative case series study: trial rasp position versus SL-PLUS◇ MIA Ti/HA femoral hip stem position

Protocol Number:	15-4567-03
Protocol Date:	07 Sep 2015
Protocol Version:	1.0
Study Product Name:	SL-PLUS◇ MIA Ti/HA femoral hip stem
Sponsor:	Smith & Nephew Orthopaedics AG Oberneuhofstrasse 10d 6340 Baar Switzerland

Table of Contents

ABBREVIATIONS & DEFINITIONS

AE	Adverse Event
ADE	Adverse Device Effect
AP	Anterior-posterior
ASIS	Anterior Superior Iliac Spine
CAPA	Corrective and Preventive Action
CCD angle	Caput-collum-diaphyseal angle
COV	Close Out Visit
CRF	Case Report Form
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFU	Instructions for Use
IMV	Interim Monitoring Visit
PI	Principal Investigator
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SIV	Site Initiation Visit
SQV	Site Qualification Visit
THA	Total Hip Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect

PROTOCOL SYNOPSIS

Title of Study:	Intraoperative case series study: trial rasp position versus SL-PLUS© MIA Ti/HA femoral hip stem position
Study Type:	Post-market, Evidence collection
Study Device:	SL-PLUS© MIA Ti/HA femoral hip stem
Indications:	• Advanced hip joint wear due to degenerative, post-traumatic or rheumatoid arthritis • Fracture or avascular necrosis of the femoral head • Follow-on conditions after previous surgery such as osteosynthesis, joint reconstruction, arthrodesis, hemiarthroplasty or total hip replacement.
Study design:	Observational, single arm, prospective, multi-center, case series study
Study Objective:	The study objective is to evaluate if there is a difference between the position of the last trial rasp and the final implant position of the SL-PLUS© MIA Ti/HA femoral hip stem.
Primary Endpoint:	Mean difference between the position of the last trial rasp and the final implant position as measured by an intraoperative fluoroscopic measurement
Secondary Endpoints:	Discrepancy of leg length after total hip arthroplasty Intraoperative complications
Length of Study:	3 months enrollment period = total study duration
Number of Sites:	up to 4 sites
Sample Size:	40
Inclusion Criteria:	Subject: • requires primary THA with the SL-PLUS© MIA Ti/HA femoral hip stem • is at least 21 years of age at the time of surgery • is skeletally mature in the PI's judgement • has consented to participate in the study by signing the Ethics Committee (EC) approved Informed Consent Form (ICF)
Exclusion Criteria:	Subject: • requires the use of a ceramic-on-ceramic bearing • has infections, acute or chronic, local or systemic • has severe muscle, nerve or vascular diseases that endanger the respective limb • has lack of bone substance or defective bone quality that jeopardizes the stable seating of the prosthesis • has any concomitant disease that may jeopardize implant function • has a known allergy to study device or one or more of its components • requires a revision surgery and has extensive bone defects • has diagnosis of an immunosuppressive disorder • is pregnant

1. BACKGROUND AND STUDY RATIONALE

As the incidence of joint disease continues to increase, an ever growing percentage of the affected population will undergo total hip arthroplasty (THA). With increasing life expectancy the demand on these hip arthroplasties is rising [1].

The success of the hip implant is directly linked to the correct position of the femoral stem. A malposition of the femoral stem may cause leg length differences, tension problems, increased risk of luxation, increased risk of impingement and increased wear which may be followed by early loosening.

Konyves et al. examined leg length inequality in 90 patients after THA. 62% of patients were observed having a leg length discrepancy after THA being associated with back pain, gait disorders and following general patient dissatisfaction. The authors further showed that in 98% of patients with leg length discrepancy, the discrepancy occurred in the femoral component strengthening the importance of appropriate placement of the femoral component [2].

The correct position of an uncemented hip stem is planned preoperatively. During surgery, the final position of the rasp should correspond to the preoperatively determined position and the same position should be adopted by the uncemented femoral stem [3].

Barink et al. examined this rasp-stem correspondence for two different rasp-stem systems in a laboratory study. They observed an average rasp-stem mis-match in three orthogonal directions smaller than 2mm for both the CLS system (Centerpulse/Zimmer Warsaw, IN, USA) and the CBC-T system (Mathys, Bettlach, CH). Based on good long term results documented for the CLS system, the authors considered the measured difference as being of very low clinical relevance [3].

In contrast, Hozack et al. showed that malpositioning of the stem is not a rare event in real life surgeries. Hozack et al. showed by observation of 100 uncemented THA with the modular Taperloc prosthesis (Biomet, Warsaw, IN, USA) that the preoperatively planned stem position could not be achieved for all cases. In 19 cases the neck length needed to be adapted after insertion of the femoral stem to achieve stability or avoid a leg length difference [4].

As indicated by Hozack et al., femoral malposition can be corrected to some degree by the selection of the appropriate components when using a modular hip system. Possibilities for correction of femoral malposition are more limited when using a mono-block system. Although small differences in the position between the final rasp and the stem are not of clinical significance, femoral malpositioning should be avoided to the highest degree possible as it forms a potential source of clinical complications [3].

The SL-PLUS® MIA Ti/HA femoral hip stem is a dual-tapered straight stem with a rectangular cross section. The SL-PLUS® MIA Ti/HA stem belongs to the SL-PLUS® family and is based on the SL-PLUS® standard stem.

The Ti/Ha coating causes an oversize of 0.7mm compared to the size of the rasp which might prevent the implant from being inserted as deeply as the rasp [5].

The purpose of this study is to evaluate if there is a difference between the final position of the femoral stem and the last trial rasp when using the SL-PLUS® MIA Ti/HA femoral hip stem with the appropriate set of instruments. In case a difference is detected this study also serves to quantify the difference in rasp and stem position for the SL-PLUS® MIA Ti/HA femoral hip stem.

2. STUDY OBJECTIVES

The study objective is to evaluate if there is a difference between the femoral position of the last trial rasp and the final implant position of the SL-PLUS© MIA Ti/HA femoral hip stem.

2.1. Primary Endpoint

The primary endpoint is the mean difference D between the position of the last trial rasp and the final implant position of the SL-PLUS© MIA Ti/HA femoral hip stem. The difference D is determined by analyzing standardized fluoroscopic images taken during surgery.

The difference D is given in mm and is defined as $D = x_1 - x_2$ with x_1 being the distance between the shoulder of the trial rasp and the tip of the greater trochanter and x_2 being the distance between the shoulder of the implant and the tip of the greater trochanter.
The distance to be measured is shown in Figure 1: Example of pre-operative planning.

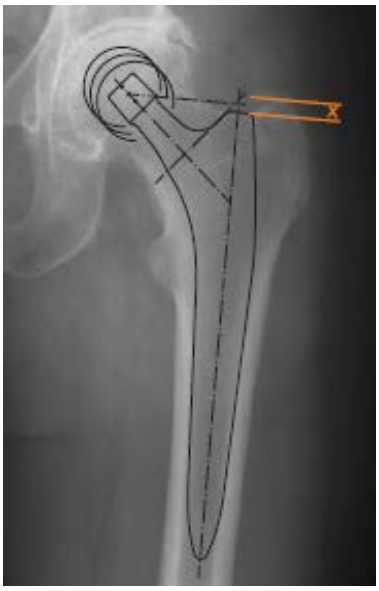

Figure 1 Pre-operative planning: x = distance between shoulder of implant and the tip of the greater trochanter [mm]

The diameter of the trial head and the final ball head will be measured to calibrate the size of the digital image.

The study hypothesis is defined as:

H_0: The null hypothesis is that there is no mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS© MIA Ti/AH femoral hip stem.

H_1: The alternative hypothesis is that there is a mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS© MIA Ti/AH femoral hip stem.

2.2. Secondary Endpoints

The secondary endpoints include a measurement of leg length discrepancy preoperatively and after insertion of the SL-PLUS© MIA Ti/HA femoral hip stem. In addition, intraoperative complications will be collected.

3. STUDY DESIGN

This is an observational, single arm, prospective, multi-center, case series study to collect intraoperative data from 40 subjects implanted with the SL-PLUS® MIA Ti/HA femoral hip stem at 4 sites in Europe.
Data from eligible subjects, who have provided written and informed consent for the collection of their coded data, will be recorded on specially designed case report forms (CRFs).
No follow-up visits after surgery are planned for study participants. Therefore, total study duration for study participants is completed with surgery.

A final data analysis describing the study outcome is planned after completion of study assessments.

4. STUDY DEVICE

The SL-PLUS® MIA Ti/HA femoral hip stem is a dual-tapered straight stem with a rectangular cross section. The SL-PLUS® MIA Ti/HA stem belongs to the SL-PLUS® family and is based on the anchorage principles of the SL-PLUS® stem.
The SL-PLUS® MIA Ti/HA stem has a minimal invasive surgery-friendly design allowing the rasps and the stem to be introduced into the bone in a curved manner. This allows reduction of bone resection in the trochanteric region, minimizes the risk of fracture, maximizes preservation of the tendon insertions and protects muscles and skin.
The SL-PLUS® MIA Ti/HA stem has a Ti/HA multi layer coating in the proximal area of the stem leading to accelerated and increased bone on-/in- growth with the aim of avoiding development of radiolucent lines by enhancement of load transmission in the metaphyseal region.

The SL-PLUS® MIA Ti/HA stem is made from Ti6Al7Nb Titanium Aluminium Niobium alloy. Two offset options are available. The standard stem is available with a Caput-collum-diaphyseal angle (CCD) of 131° and the lateral stem is available with a CCD angle of 123°.
The standard stem is available in 128mm to 188mm length. The lateral stem is available in 136mm to 188mm length.

4.1. Surgical Technique

All study related procedures with the SL-PLUS® MIA Ti/HA femoral hip stem must be performed according to the recommended surgical technique described in the labeling and in the instructions for use (IFU).
Surgeons selected to participate in this study will be familiar with implanting SL-PLUS® MIA Ti/HA femoral hip stem and have evidence of training and expertise in the study procedure.

4.2. Device Accountability

Device accountability is not required to be recorded as sites will be expected to use products from their own stock. Device information will be recorded on the CRF and chart sticks will be kept within the CRF to document the devices used.

5. STUDY POPULATION

5.1. Subject Screening & Enrollment

To eliminate the potential for selection bias, Investigators should consecutively pre-screen all subjects undergoing THA with the SL-PLUS® MIA Ti/HA femoral hip stem. In order to do so, only the existing information obtained per standard routine medical procedures will be used. No study-specific screening procedures, activities or questionnaires will be performed during pre-screening.
Once a subject has completed the informed consent procedure and signed the Informed Consent Form (ICF), the Principal Investigator (PI) or delegated study research staff can complete the screening process with the subject. All potential subjects who undergo the screening process will be documented on a Screening and Enrollment Log, on which reasons for exclusion from or denial to participate should be noted.

5.2. Subject Inclusion Criteria

Subject:

- requires primary THA with the SL-PLUS® MIA Ti/HA femoral hip stem
- is at least 21 years of age at the time of surgery
- is skeletally mature in the PI's judgment
- has consented to participate in the study by signing the EC approved ICF

5.3. Subject Exclusion Criteria

Subject:

- requires the use of a ceramic-on-ceramic bearing
- has infections, acute or chronic, local or systemic
- has severe muscle, nerve or vascular diseases that endanger the respective limb
- has lack of bone substance or defective bone quality that jeopardizes the stable seating of the prosthesis
- has any concomitant disease that may jeopardize implant function
- has a known allergy to study device or one or more of its components
- requires a revision surgery and has extensive bone defects
- has diagnosis of an immunosuppressive disorder
- is pregnant

6. STUDY PROCEDURES

6.1. Study Schematic

The study duration for each subject is defined as the time between signing the ICF and time of completion of surgery (transfer to general ward). The intervals and schedule of events are provided in Table 1.

Table 1 Schedule of events

Schedule of events	Pre-Operative	Surgery / Peri-Operative
Patient Information and Informed Consent	√	
Inclusion/Exclusion Criteria	√	
Demographics/Medical History	√	
Radiographic assessment	√	
Operative Data Collection		√
Fluoroscopic assessment		√
Measurement of leg length discrepancy	√	√
Adverse Event Assessment	√*	√
End of Study/Exit		√

*if applicable

The following algorithm should guide through the steps of pre-screening, screening, enrollment and study conduct in accordance with sections 6 Study Procedures and 7 Subject Completion and Disposition of this protocol.

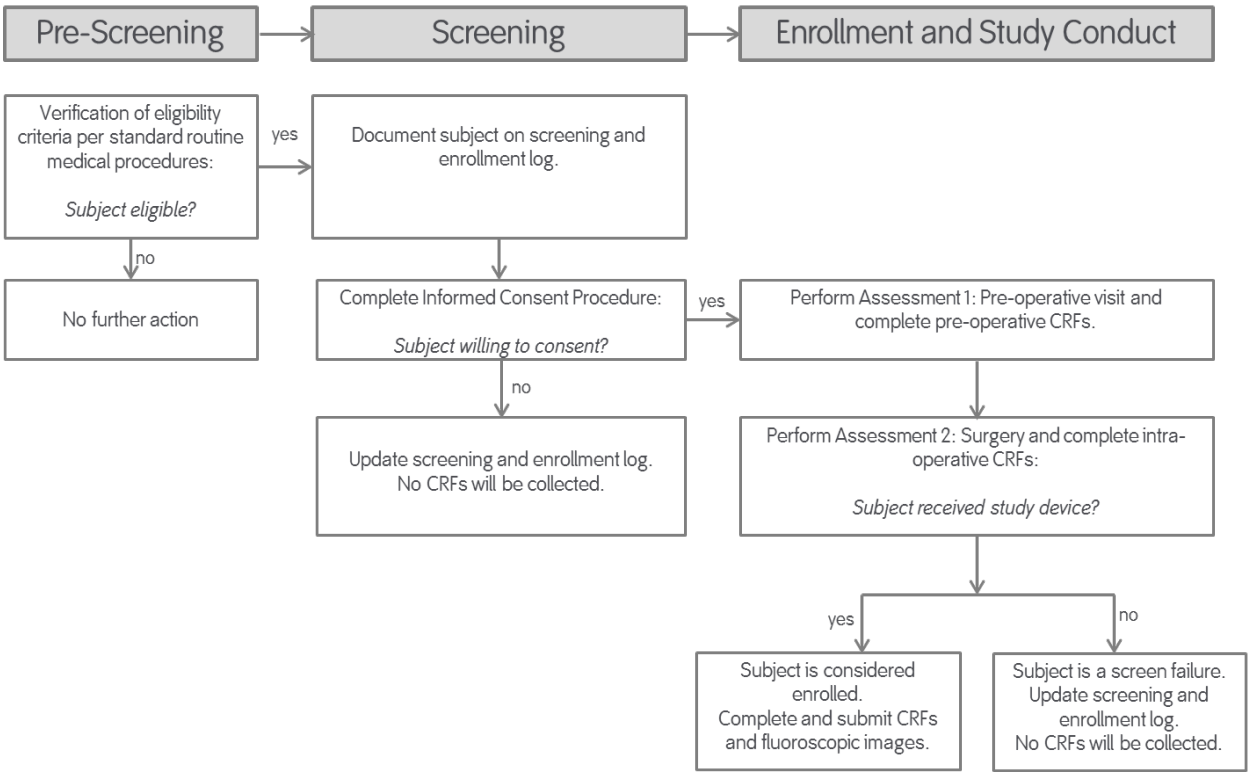

Figure 2 Overview of pre-screening, screening, enrollment and study conduct

6.1.1. Assessment 1: Pre-Operative Visit

During the pre-operative visit a standard anterior-posterior (AP) pelvic hip radiograph will be taken.
The AP view should include full pelvic overview. The pre-operative radiograph will be taken for diagnostic purposes and THA planning. The Investigator will analyze the pre-operative radiograph and collect the following information on the appropriate CRF:

- diagnosis for THA
- bone quality according to Dorr et al. [6]
- distance x between the shoulder of the implant and the tip of the greater trochanter, reference Figure 1, measured during preoperative planning

Based on the pre-operative planning, implant sizes planned to be used during THA will be recorded on the CRF.
The leg length difference will be measured by the Investigator or designee during the preoperative physical examination. The length of each lower extremity is determined in cm by measuring the distance between the anterior superior iliac spine (ASIS) and the medial malleolus by using a measuring tape with the subject in supine position [7]. Measured distances will be recorded on the appropriate CRF.

6.1.2. Assessment 2: Surgery

During surgery two fluoroscopic AP images will be taken showing the position of the final trial rasp with trial head and the final position of the implanted stem with final ball head. The joint will be reduced at the time the images are taken. The AP view should include the full articulation of the operated side with the greater trochanter and the shoulder of the implant / rasp visible.
The images will be de-identified and submitted to an assigned medical person for centralized analysis after surgery. The medical person will be assigned by S&N to analyze the fluoroscopic images and to collect the following information on the appropriate CRF:

- distance x_1 between the shoulder of the trial rasp and the tip of the greater trochanter
- distance x_2 between the shoulder of the implant and the tip of the greater trochanter
- diameter of trial head and final ball head

In addition, the following data will be collected during surgery and recorded on the appropriate CRF:

- It will be recorded what type of rasping instrument was used for femoral preparation giving the following options:
    - Slap hammer
    - Woodpecker
    - Mallet
    - Combination
- Information of implanted devices will be recorded on the CRF and by collecting the chart sticks on the CRF.
- The type of the surgical approach will be collected.
- During surgery it will be recorded if the surgeon needed to correct the position of the stem compared to the final rasp and which one of the following methods was used:
    - Smaller ball head length
    - Larger ball head length
    - Removal of stem and enlargement of femoral bed with last trial rasp
    - Other methods

All intraoperative complications will be recorded as outlined in section 8 Safety reporting.

The leg length difference will be measured by the Investigator or designee peri-operatively shortly after surgery before transfer of the subject to the general ward. The length of each lower extremity is determined in cm by measuring the distance between the ASIS and the medial malleolus by using a measuring tape with the subject in supine position. Measured distances will be recorded on the appropriate CRF.

7. Subject Completion and Disposition

7.1. Screening

Patients considered potential candidates for the study based on the Investigator's initial assessment (pre-screening) must sign an EC approved ICF prior to any study activities. The PI or delegated study research staff will review the eligibility criteria and if determined as eligible will complete the first study assessment (Assessment 1: pre-operative visit) with the subject.

7.2. Enrollment

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

7.3. Conditions for Study Termination

Reasons for termination of study participation are described below.

A. Screening Failure

Subjects who have provided informed consent but did not receive the study device are considered screen failures. The reason for screening failure must be captured on the Screening and Enrollment Log maintained in the Investigator Master File. No CRFs will be collected.

B. Voluntary Withdrawal

Study participation is voluntary and subjects may withdraw at any point during the study without giving their reason for doing so. CRFs are collected until time point of withdrawal.

C. Subject Termination by Investigator

The Investigator should withdraw subjects from the study in case the study device cannot be implanted during surgery for any reason.
Subjects that do not receive the study device are not considered as enrolled and will be documented on the Screening and Enrollment Log.

D. Study Termination

The Sponsor may choose to discontinue the study at any time. In which case, the subjects will be followed up according to the standard practice of the site.

E. Study Site Discontinuation

A specific study site in this multicenter study may also warrant termination under the following conditions:

- non-compliance to Good Clinical Practice (GCP) or protocol
- failure to enroll subjects

- inaccurate or incomplete data
- unsafe or unethical practices
- safety or performance considerations

In this case, enrolled subjects will be followed up according to the standard practice of the site.

8. SAFETY REPORTING

Adverse events and device deficiencies, noted by study staff and reported by the subject, and occurring from the time of study device implantation through to study completion should be recorded on the appropriate CRFs and reported as below.

8.1. Definitions for safety reporting

A. Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device [8].
This definition includes:

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

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

B. Serious Adverse Event (SAE)

A SAE is an adverse event that [8]:

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

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

C. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device [8].

This definition includes:

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

D. Serious Adverse Device Effect (SADE)

An SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event [8].

E. Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or the clinical investigation plan [8, 9].

F. Device Deficiency

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

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

8.2. Safety: Investigator's Responsibilities

Investigators shall record AEs and DDs, together with an assessment, in the subject's source data. Following, Investigators are responsible for documenting AEs and DDs on the appropriate CRF and submitting them to the Sponsor according to the timelines described below.
AEs must be recorded in standard English medical terminology.

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

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

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

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

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

8.3. Timelines for Submission of Safety Information:

The timelines begin when the Investigator becomes aware of the event.
The Investigator will report to the Sponsor:

- As soon as possible, but no greater than 24 hours upon becoming aware of the event:
  - SAEs
  - SADEs
  - USADEs
  - DDs that could have led to a SADE:
    - if suitable action had not been taken
    - if intervention had not been made, or
    - if circumstances had been less fortunate
  - Re-operation at the study site. Sponsor will provide an explant retrieval kit on becoming aware of a revision and ask the Investigator to return any revised components for retrieval analysis.

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

The PI will be responsible for reporting to the EC of the study site and to the regulatory authorities, SAEs, SADEs and DDs that could have led to a SADE, as required by the national regulations.

8.4. Safety reporting: Sponsor's Responsibilities

Sponsor will provide progress reports on safety events to the Investigator to report to the EC as required.
In the case of multicenter studies, Sponsor will inform all Investigators in writing of all SAEs that were reported by all sites throughout the clinical investigation and based on perceived risk.
The Sponsor will also, in case of SADEs and DDs that could have led to SADEs, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

9. STATISTICAL PROCEDURES

9.1. Hypothesis and Sample size calculation

The following hypotheses will be tested:

H_0: The null hypothesis is that there is no mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS® MIA Ti/AH femoral hip stem.

H_1: The alternative hypothesis is that there is a mean difference between the position of the last trial rasp and the final implant position of the SL-PLUS® MIA Ti/AH femoral hip stem.

The study hypothesis can be written as:
H_0: $\mu=0$ vs. H_1: $\mu \neq 0$

In 2007, a non-published cadaver test was performed to measure the difference D between the position of the last trial rasp and the implant position of the SL-PLUS® MIA Ti/AH femoral hip stem. A total of 4 femoral hip stems were implanted into the cadaveric femur. The range of the measured difference was found to be between 0mm and 6mm. However, it is most likely that the maximum difference will be greater 6mm when more cases are studied. To compensate for the small number of evaluated cases, the anticipated variation in D will be extended to 10mm with an estimated standard deviation of 2.5mm. A correlation ρ between the distances x_1 and x_2 is certainly positive but it is unknown how strong the correlation is. The standard deviation sd of the difference D has the following relationship with the standard deviations sd_1 and sd_2 for distances x_1 and x_2:

$$sd^2 = sd_1^2 + sd_2^2 - 2\rho sd_1 sd_2$$

Since $\rho>0$ and assuming that $\rho=0$ will lead to a larger sd and therefore a larger sample size. If assumed that $sd_1=sd_2$, then $sd^2=2sd_1^2$. So assuming sd_1 and sd_2 being equal, the sd will also lead to a larger sample size. Therefore, assuming that the correlation is zero and allowing for both standard deviations sd_1 and sd_2 to be 2.5mm is a conservative approach for computing sample size.
According to orthopaedic surgeons, the maximum difference between the position of the rasp and implant without clinical significance is considered to be 2mm. The standard deviations of sd_1 and sd_2 are estimated as approximately 2.5mm estimated based on the assumptions above and data for the range of difference..
The sample size calculation is based on a two-sided test. The significance level and power of the study are chosen to be 0.05 and 0.90; the minimum mean difference Δ is identified as 2 mm; the standard deviations sd_1 and sd_2 are 2.5mm; the correlation between x_1 and x_2 is set to 0. The following formula can be used to calculate the sample size:

$$N \geq \frac{2(T_{N-1,\alpha/2} + T_{N-1,\beta})^2 sd^2}{\Delta^2}$$

The SAS POWER procedure is used to compute the sample size and at least 35 subjects are needed for the study.

9.2. Statistical Analysis

All subjects who meet the study inclusion and exclusion criteria will be included in the statistical analysis. Statistical analyses will be conducted for demographics, pre-operative information, surgical information and safety data. Demographics will include, but not limited to, gender, age, weight, height, BMI. Pre-operative information and surgical information will include any data collected as defined in this protocol. Safety data will

include adverse events, serious adverse event, adverse device effect, serious adverse device effect, unanticipated serious adverse device effect, and device deficiency.
Descriptive statistics for continuous variables will include mean, median, minimum, maximum, standard deviation, and 95% confidence interval, if appropriate. Descriptive statistics for discrete variables will include count and percentage.
Subgroup analyses will be provided if they are necessary. The following sections define the details of primary endpoint and secondary endpoints analyses.

9.2.1. Primary Endpoint Analysis

If the difference between x_1 and x_2 measured from fluoroscopic images approximately follows a normal distribution, then a two-sided paired T test will used to test the mean. The test statistic is a t-score defined by the following equation:

$$T=\overline{D}/(sd/\sqrt{N})$$

where

$$\overline{D}=N^{-1}\sum_{i=1}^{N}(x_{i1}-x_{i2})$$

$$sd=\sqrt{\sum_{i=1}^{N}(x_i-\overline{D})^2/(N-1)}$$

$x_i = x_{i1} - x_{i2}$, i=1, … N.

The SAS TTEST procedure will be used to perform the paired T test. If the difference does not follow a normal distribution, then the signed rank test will be used to test the hypothesis. The SAS UNIVARIATE procedure will be used to perform the signed ranked test.

The null hypothesis will be or not be rejected based on corresponding observed p value from the test above. An alpha value of 0.05 will be used in the hypothesis testing.

9.2.2. Secondary Endpoint Analysis

Descriptive analyses will be presented for the secondary endpoints of leg length discrepancy and intraoperative complications.

9.3. Missing Data

The primary endpoint is an intraoperative measurement so there is no expectation for missing data due to lack of follow up. However, the primary endpoint could be missing due to other issues such as unreadable images. Allowing for 12% missing data, a total sample size of 40 cases is needed in the study.

10. Ethical Considerations

10.1. Ethical Approval

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

10.2. Protocol Amendments

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

10.3. Informed Consent

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

10.4. Risk – Benefit Analysis

A. Study Related Risks

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

- This study involves the use of x-ray and fluoroscopic evaluation. X-ray exposure is cumulative over a lifetime and total exposure should be kept to a minimum. However, if the x-ray exposure when participating in the study is equivalent to the exposure the subject would receive if they chose not to participate in the study, there is no additional risk associated with this study.
- As a result of participating in the study there could be a risk of loss of protected subject information confidentiality. All applicable confidentiality standards and data protection and privacy laws will be followed by the Sponsor to ensure that data collected is handled in confidence. Data will be coded and handled only by appropriately qualified and authorized personnel.

Risks related to the general surgical procedures and exposure to x-ray for preoperative planning are not considered here because these risks are equivalent whether the subject participates in the study or not.

B. Study Related Benefits

Because the surgery and all the follow-up visits are the same as when the subject would not participate in this study, there are no additional medical benefits associated by participating in this study. The information gained from this study may help to improve the existing instruments used for the implantation of the SL-PLUS® MIA Ti/HA femoral hip stem and in consequence improve the treatment of patients that need to undergo THA.

11. MONITORING PROCEDURES

11.1. Source Documentation

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject (source documents). Examples of source documents are: hospital records, clinic and office charts, memoranda, dispensing records, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection reports and shipment records, and research subject files.
CRFs may be used as source documents if they represent data collected for the study and are the location that data is initially recorded.

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

11.2. Direct Access

This study may be monitored by the Sponsor or a qualified person designated by the Sponsor. This qualified person could be an employee of the Sponsor or of a contract research organization (Sponsor's agent).

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

11.3. Site Qualification Visit (SQV)

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

11.4. 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 Study Agreement**: 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 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:** all participating Investigators are required by ISO 14155 to provide details of conflict of interest (including financial, if applicable) according to local regulations. This information must be updated promptly by the Investigator and submitted to the Sponsor if any changes occur through the duration of the study and for one year following completion of the study.

11.5. Site Initiation Visit (SIV)

A SIV to provide training on the specifics of the study, site obligations and expectations of study conduct will be performed by the Sponsor following execution of the Clinical Study Agreement and documented EC approval.

11.6. Interim Monitoring Visits (IMVs)

Due to the short length of the study no IMVs will be performed.

11.7. Sponsor Audits and Regulatory Inspection

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.

11.8. Close Out Visit (COV)

A study COV 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 the Investigator Master File 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 EC reporting requirements.
During the COV the monitor will further:

- verify the informed consent process
- perform source data verification
- verify that source documentation is complete and available
- ensure compliance with the protocol

11.9. Documentation of Site Visits

Activities associated with a monitoring visit (SQV, SIV, COV) will be documented by the monitor. This includes:

- monitor visit log on site
- a Follow-Up letter to the Investigator following each visit summarizing the visit and detailing any site deficiencies and action items to clarify or address issues noted

11.10. Data Handling and Record Keeping Requirements

CRFs will be supplied by the Sponsor. Subjects will be identified by a study number and subject identification code. Only the Investigator site will have the key to identify individual subjects.
The Investigator is responsible for the timely and accurate completion of CRFs. All documents related to the study must be securely archived at the study site or in a central archive.
Data required according to this protocol are to be recorded on the CRFs at the time of the scheduled visits. Once a subject is enrolled, completed CRFs should be sent to the Sponsor, either by fax or by e-mail, as soon as possible, and no later than 10 working days upon completion of the CRFs.

11.11. 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 date the study is terminated or completed. 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.

12. DEVIATIONS FROM PROTOCOL

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

12.1. Protocol Deviation Reporting Requirements

Deviations must be reported to the Sponsor through the specially designed Protocol Deviation Log as soon as reasonably possible.

When protocol deviations affect the scientific soundness of the study, or the rights, safety or welfare of the study subjects, the Investigator must also report protocol deviations to the EC of the study site. It is the responsibility of the PI to inform the EC of the incident, per local requirements. The local EC should be consulted on protocol deviation reporting requirements.

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

13. PUBLICATION POLICY

13.1. Multicenter Publication

The Sponsor may invite the Investigator to participate in a multicenter publication of the study results, in which case it will be ensured that the documents submitted for publication comply with the publisher's requirements for authors and contributors. If the publisher has no such requirements, it will be ensured that the publication meets the authorship and contributorship requirements as stated in the current Smith & Nephew Global Policy and Procedure relating Scientific Disclosures. Also, the Sponsor will select a publisher based on mutual agreement with the Investigators, who are invited to participate in the publication.

13.2. Investigator Publication

The Investigator may publish his/her own data subject to the following restrictions:

- the multicenter manuscript must be published prior to Investigators publishing their own data;
- the manuscript shall be submitted to the Sponsor for review prior to submitting the manuscript for publication;
- the manuscript must reference the study multicenter manuscript.

13.3. Authorship

Unless otherwise required by the journal of publication or the forum in which a presentation is made, authorship will comply with ICMJE current Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. ICMJE recommends that authorship be based on the following criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and
- Drafting the work or revising it critically for important intellectual content; and
- Final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

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

BIBLIOGRAPHY

1. Hart, J.A., *Joint replacement surgery.* Med J Aust, 2004. **180**(5 Suppl): p. S27-30.
2. Konyves, A. and Bannister, G.C., *The importance of leg length discrepancy after total hip arthroplasty.* J Bone Joint Surg Br, 2005. **87**(2): p. 155-7.
3. Barink, M., et al., *How close does an uncemented hip stem match the final rasp position?* Acta Orthop Belg, 2004. **70**(6): p. 534-9.
4. Hozack, W.J., Mesa, J.J., and Rothman, R.H., *Head-neck modularity for total hip arthroplasty. Is it necessary?* J Arthroplasty, 1996. **11**(4): p. 397-9.
5. *Surgical Technique SL-PLUS MIA Cementless Fenoral Hip System*, S.N.O. AG, Editor. 2015.
6. Dorr, L.D., et al., *Structural and cellular assessment of bone quality of proximal femur.* Bone, 1993. **14**(3): p. 231-42.
7. Sabharwal, S. and Kumar, A., *Methods for assessing leg length discrepancy.* Clin Orthop Relat Res, 2008. **466**(12): p. 2910-22.
8. *Clinical investigation of medical devices for human subjects - Good clinical practice (ISO 14155:2011)*, in *SN EN ISO 14155*.
9. *Code of Federal Regulations Title 21.* 2014. **21CFR812**.