A Prospective, Multi-Center, Non-Randomized, Safety and Efficacy Clinical Study of the LEGION◇ Primary Knee System for Primary Total Knee Replacement in Subjects with Degenerative Knee Disease

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Study Product: LEGION◇ Primary Knee System

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INTRODUCTION

As the incidence of joint disease continues to increase, an ever growing percentage of the affected population may choose to have total knee arthroplasty (TKA).[1, 2, 3, 4] This recent upward trend appears to be directly related to the prevalence of certain health factors. Specifically, longer life spans, rising obesity rates, and increasing physical activity levels in relatively younger populations are all examples of health factors that may significantly contribute to knee degeneration.[3, 5, 6] While strategies such as weight reduction, lifestyle change or drug therapy may offer temporary relief from the symptoms of knee degeneration, TKA remains the standard of care for subjects experiencing significant losses in quality of life due to advanced osteoarthritic disease.[1, 3]

Contemporary advances in TKA are allowing for improved surgical techniques and implant designs. Given such a positive track record, surgeons have relatively high expectations for device safety and function. Moreover, both surgeons and subjects alike are placing increasing emphasis on the recovery of function postoperatively.[8, 9, 10, 11] Therefore, once a device is introduced into a market, research focusing on clinical outcomes is essential in order to assess whether or not surgeon and subject expectations are being met. In addition, this data can be used to support the design rationale of future devices.

Factors affecting clinical outcomes following TKA include subject age, subject activity level, preoperative range-of-motion, gender, anatomic variation, preoperative joint pathology and metal sensitivity. Clinically successful devices must be versatile in order to address variation between cases.

I. STUDY OBJECTIVES

The objective of the current study is to establish the safety and efficacy of the LEGION® Primary Total Knee System at each postoperative time point using the following parameters:

A. Efficacy Criteria

- The Knee Society Clinical Rating System [15] (KSS) will provide separate measures of knee pain and subject function. The primary efficacy outcome measure will be passive flexion. Range of motion for the KSS score will be determined using a goniometer.
- The Knee Osteoarthritis Outcomes Score (KOOS) will be used as a self-administered measure of subject health status. Specifically, the KOOS score will allow for the assessment of pain, stiffness, and overall physical function.
- Serial radiographic follow-up of study subjects by the Clinical Investigator using the Knee Society Roentgenographic Evaluation and Scoring System. [16] The purpose of the radiograph evaluation at short-term follow-up is to assess baseline knee alignment. At mid-term follow-up and long-term follow-up, the focus of the

radiographic evaluations are to assess any evidence of loosening as indicated primarily by radiolucencies $\geq$ 2mm; lack of evidence of surface wear or particulate debris generation as indicated by early osteolysis, implant migration, or other clinical or radiographic abnormalities. A flexed lateral radiograph will be taken and used to obtain the flexion angle.

B. Safety Criteria

- Surgical and knee-related adverse events, including revision, will be reported during the conduct of this study.
- The frequency of revisions and knee related adverse events.

C. Health Economic Criteria

- Intraoperative data, including operative time, blood loss and surgical related complications will be assessed.

II. DEVICE DESCRIPTION AND PROCEDURES

The LEGION® Total Knee System is a comprehensive system designed to allow surgeons to address straightforward primary to complex knee arthroplasty. The LEGION® Total Knee System consists of oxidized zirconium or cobalt-chrome primary femoral components, titanium primary tibial components, and a polyethylene patella. In addition, conventional and cross linked polyethylene tibial inserts are available in both traditional and high flexion options. The resulting product is sufficient to accommodate a wide range of clinical applications.

Various instruments are required that allow the surgeon to assemble the components and prepare the bones to accept the implants. These instruments are routinely utilized as part of the standard LEGION® Total Knee System surgical procedure. Instruments of the device system are typically manufactured from stainless steel meeting applicable American Society for Testing and Materials (ASTM) standards. Handles of some instruments are made of plastic or aluminum. Additionally, various general surgical instruments and bone shaping tools such as chisels, saws, knives, curets, drills, etc. may be used that are a generic component of any orthopaedic operative procedure.

III. RISKS

There are risks associated with any knee replacement procedure that may result from the surgery itself, the device that is implanted, or the instrumentation used to implant the device. This study does not involve investigational products as all components have been cleared for use by the FDA and are commercially available. Product labeling is available to outline product risks for this device. The risk of this surgery should be explained to the subject as part of the consent for surgery.

Study assessment includes radiographic evaluation. Risks may be associated with radiographic evaluation as part of the routine care involving TKA procedures and exposure to more radiation due to the increased number of x-rays the subject will undergo in follow-up. X-ray exposure risk is cumulative over a lifetime, and total exposure should be kept as low as possible. Additional risks associated with this study include the loss of confidentiality and the risks associated with blood collection. Blood collection procedures require that a sterile needle be placed into a vein. This may be associated with some discomfort as the needle is inserted into the vein. Other complications may occur such as blood or fluid leaking or collecting under the skin and forming a bruise, mild irritation of the skin or tissue in the area, and infection at the blood draw site.

The risks associated with this study include:

- Loss of confidentiality
- Exposure to additional radiation due to the increased number of x-rays patient will undergo during follow-up visits.

X-ray exposure risk is cumulative over a lifetime, and the total should be kept as low as possible.

IV. STUDY DESIGN

This is a prospective, consecutive series, multi-center clinical study of the LEGION® Total Knee System. The study design was selected to assess the safety and effectiveness profile of the LEGION® Total Knee System in subjects with degenerative knee disease requiring primary total knee replacement.

Subjects meeting the entrance criteria specified in this protocol will be approached to participate in the study and enrolled sequentially. Any consenting subjects meeting the inclusion criteria are not to be excluded unless they do not consent to participate. A nonrandomized, consecutive series of up to 138 subjects will be enrolled at a maximum of 8 research sites, with an expectation of 18 subjects (up to a maximum of 28 subjects) to be enrolled at each site. When 138 subjects are enrolled from all sites, enrollment will be stopped, regardless of the number contributed from each site. Sites will be selected for participation in the study at the discretion of Smith & Nephew.

Follow-up clinical assessments will be at Operative/Discharge, 3 months, 1 year, 2 years, 3 years, 5 years, 7 years and 10 years. Each subject will receive a standard radiographic evaluation at discharge that will be used for baseline analysis. Additional radiographic analysis will be performed at Operative/Discharge, 3 months, 1 year, 2 years, 3 years, 5 years, 7 years and 10 years.

<u>The primary endpoint will be:</u>

- Cumulative percent survival

The secondary endpoints will be:

- Surgical and device related adverse events
- Knee Society Score (KSS)
- Knee Osteoarthritis Outcome Score (KOOS)
- Radiographic evaluation

V. STUDY POPULATION

A. Subject Selection Criteria

The subject population considered for this study is osteoarthritic subjects requiring a total knee replacement. The following inclusion and exclusion criteria will be used to identify study candidates. It is very important that every subject who meets these entry criteria be enrolled into the study and that no subjects be disregarded or omitted for other reasons. A method should be established upon beginning the study whereby all potential study candidates are given the opportunity to participate sequentially.

B. Inclusion Criteria

Subjects must meet all of the inclusion criteria:

1. Subject is a candidate for the LEGION® Primary Knee System according to the instructions for use;
2. Subject is of legal age and skeletally mature;
3. Subject is willing to sign and date an ethics-approved consent form and participate in the study;
4. Subject is willing to be available for ten-year follow-up postoperatively.

C. Exclusion Criteria

Subjects must not meet any of the exclusion criteria:

1. Subject with immunosuppressive disorders;
2. Subject has grossly insufficient femoral or tibial bone stock;
3. Subject has an active localized or systemic infection;
4. Subject is pregnant;
5. Subject psychological or neurological conditions that would impair the subject's ability or willingness to restrict activities or follow medical advice during the course of this study;
6. Subject is a prisoner.

VI. STUDY PROCEDURES

A. Prior to Study Initiation

The following documents must be provided to Smith & Nephew prior to study initiation:

1. Copies of the IRB approval letter and IRB approved informed consent for each institution used by the Investigator for the clinical study.
2. A signed Statement of Investigator.
3. A current, signed, dated CV and medical license for the Principal Investigator documenting the location where the study will be conducted.

B. Subject Enrollment

1. Screen Subject – All subjects who present with total knee osteoarthritis requiring joint replacement will be screened for eligibility in the study based on physical exam and radiographic evaluation of the joint.
2. Informed Consent – If the subject meets all inclusion and exclusion criteria, a consent form is presented to the subject. If the subject elects to participate in the study, the subject must sign the consent form prior to completing any study related activities.
3. Preoperative Evaluation – After the subject meets the entrance criteria and signs the consent form, the appropriate preoperative study activities are to be completed.

C. Operative Procedures

1. Surgical Technique

   The medical device will be implanted using standard surgical technique(s), depending on the individual investigator's standard procedure. Instrumentation specific for the device will be used. A surgical technique brochure for implanting the LEGION® Total Knee System will be provided to each investigator.

2. Operative Data

   Operative data and device information will be collected. All operative adverse events will also be reported.

D. Postoperative Procedures

Adverse events occurring during the hospital stay will be reported. Discharge information will also be captured.

E. Follow-up Procedures

Subjects will be evaluated clinically at 3 months, 1 year, 2 years, 3 years, 5 years, 7 years, and 10 years postoperative. Please see Section I, "Schedule of Events" Table for details and visit windows.

All radiographic observations are to be reported on the radiographic form. Postoperative device-related and surgical adverse events are to be reported.

All reasonable efforts should be made to keep in contact with the subject for the 10 year duration of this study.

F. Radiographic Procedures

The important aspects of successful joint arthroplasty are component position, joint alignment, and the prosthesis-bone interface or fixation.

In order to assess the safety and efficacy of the current study device, radiographic evaluations will be performed during regular follow-up intervals up to the ten year postoperative visit.

It is absolutely critical that positioning errors be minimized so that accurate and consistent measurements can be taken for all device components. Radiographs are to be taken and reported Operative/Discharge, 3 months, 1 year, 2 years, 3 years, 5 years, 7 years, and 10 years postoperatively. The span of the bone-prosthesis interface obtained in these 3 views (AP/lateral/skyline) for each component is broken down into zone systems. The scoring system for each of the three components is determined by measuring the radiolucent lines (in millimeters) for each of these zones.

Any other radiograph views taken are at the discretion of the individual clinician.

G. Adverse Events

The following are definitions of adverse events:

Adverse event - any undesirable clinical occurrence in a subject, regardless of the cause

Device-related adverse event - an adverse event that is related to device use, e.g. component breakage

Unanticipated adverse device effect (UADE)- an event that is not identified in nature, severity, or frequency in the current package label or informed consent

Serious/severe adverse event - an event that is

1) Life threatening or fatal,

2) Requires or prolongs hospitalization,

3) Results in permanent impairment of a body function, or

4) Results in permanent damage to a body structure.

All postoperative device-related and surgery-related adverse events are to be reported. Specifically, all component removals (and/or revisions) whether device-related or not must be recorded. Other adverse events not listed here may be classified as device-related (or non-device-related) depending on their frequency, medical significance, and circumstance. Device-related adverse events (complications) are defined as any of the following:

- Any device implant component failure (e.g. breakage)
- Device-wear particle-induced osteolysis, inflammation, etc. Wear debris may be metal, cement, and/or HA in composition.
- Any device component experiencing dislocation, subluxation, subsidence, or migration.

All serious adverse events, life-threatening problems, or deaths that occur during or following the use of the devices during the study should be fully documented in the research record by the Investigator including the onset date, complete description of the event, severity, duration, action taken, and outcome. The event should be documented on the appropriate interval and case report form. The investigator will be responsible for notifying the reviewing ethics committee or IRB of any unanticipated adverse events. The Investigator will record all non-serious, device-related adverse events on the appropriate case report form. All adverse events must be followed until they resolve, or are considered final.

Adverse events that are serious, unanticipated and possibly device-related must be reported in detail by the Investigator to Smith & Nephew and the reviewing IRB as soon as possible, but in no event later than ten working days after the Investigator first learns of the event.

H. End of Study

Study completion status of the subject (e.g. completed per protocol, subject withdrawal, device removed, death, lost-to-follow-up, or other reason) is to be recorded. A subject having a specified objection to continuing in the study will be withdrawn. Any subject who withdraws from the study postoperatively will be considered in the data analysis up until the time of their withdrawal. Subjects lost to follow-up will be documented on the End of Study form. All reasonable efforts should be made to keep in contact with the subject for the 10 year duration of this study.

Subjects may be taken out of the study without their consent for the following reasons:

- ✓ The Investigator decides that continuing the study would be harmful
- ✓ Participants miss so many appointments that their data cannot be used in the study
- ✓ The study Sponsor (Smith & Nephew, Inc.) decides to end the study

If a subject is unwilling to return to the site for evaluation, available information may be collected on the subject's condition via telephone or correspondence. Participation in this study is completely voluntary. If any subject chooses not to participate or removes their consent at any time, subject care must continue according to the physician's standard of care. The site must document changes in subject enrollment via a de-identified summary and forward this information to the sponsor. All subjects who complete the study prematurely will be included in the data analysis up until the time of their study completion.

I. Schedule of Events

Study Activity	Preop	O/D	3 mo (± 2 mo)	1 yr (± 3 mo)	2 yr (± 6 mo)	3 yr (± 1 yr)	5 yr (± 1 yr)	7 yr (± 1 yr)	10 yr (± 1 yr)
Inclusion/exclusion Form	X	-	-	-	-	-	-	-	-
Informed Consent	X	-	-	-	-	-	-	-	-
Demographics/ Med History Form	X	-	-	-	-	-	-	-	-
Clinical KSS/KOOS	X	-	X	X	X	X	X	X	X
Operative/Discharge Form	-	X	-	-	-	-	-	-	-
Radiograph Analysis	-	X	X	X	X	X	X	X	X
Adverse Event Form	-	†	†	†	†	†	†	†	†
End of Study/Exit Form	-	-	†	†	†	†	†	†	†

† This form should be completed when necessary.

VII. DATA COLLECTION

A. Case Report Forms

Case report forms (CRF) will be used to collect the data obtained during this study. Data must be transcribed from source documentation to CRFs. Subject questionnaire data will be recorded directly onto the provided CRFs, and will not be transferred from source documentation.

The CRFs are a set of forms that include questions to record preoperative, operative, discharge, postoperative and x-ray information. A complete set of CRFs will be provided for each subject enrolled.

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

Investigators are required to fax all completed CRFs to Smith & Nephew at **(877) 515-0213,** at the appropriate intervals to ensure consistent, accurate analysis of study data. Any parameters not collected may adversely impact the quality and validity of the final results of this study. Special care should be taken to record any device-related or surgical adverse event including a complete description of their relationship to the study device.

Source Documents – Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject and each assessment (source documents).

Source data includes all information in original records and certified copies of original records of clinic findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (e.g., hospital records, clinic evaluation, transcriptions, operative notes, x-rays, radiology reports, blood collection and shipment records, research subject files, etc.)

Every data point that is found on the CRF and submitted to the Sponsor must have a corresponding source document in the subject record(s) that provides detailed evidence of the assessment. The Sponsor and its agents will be provided direct access to source documents for the purpose of verifying the clinical data submitted to the Sponsor by the investigator on CRFs.

B. Data Quality Assurance

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

The Clinical Affairs Department at Smith & Nephew, Inc. will promptly review all incoming case report forms and accompanying documentation to identify inconsistent or missing data and device-related complications. Problems with these data will result in queries to the site that should be addressed within two weeks of receipt. *It is incumbent upon the site to review all data recorded on each form prior to submission to Smith & Nephew, Inc.* To ensure the confidentiality of data, Smith & Nephew, Inc. will maintain a secure study database.

Protocol Deviation – Protocol deviation is defined as any non-adherence to the protocol or Investigational Plan. Protocol deviations will be reported to Smith & Nephew on the appropriate Case Report Form. The investigator must also report protocol deviations to the IRB as required.

Modification of the Protocol – Neither the Investigator nor Sponsor will modify this protocol without mutual agreement. After agreement to initiate the modification (in the form of a protocol amendment), the Investigator agrees not to institute this modification until instructed to do so by the Sponsor. It may be necessary to obtain applicable regulatory authority and IRB/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.

Departure from Protocol for Individual Subject in Emergency – Only in an emergency where action is necessary to protect the life or physical well-being of the subject will a departure from the protocol for an individual subject be allowed, and the departure will be for that subject only. The investigator or other physician in attendance in such circumstances will notify the IRB and contact the clinical study manager at Smith & Nephew immediately (within 48 hours) by telephone. If the study manager is unavailable, contact the next available Smith & Nephew Clinical Affairs professional.

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A decision will be made by the investigator and Smith & Nephew about whether the subject (for whom the departure from protocol was affected) is to continue in the study. Any departure from the protocol will be described in a written report by the investigator who will send the report to the IRB and Smith & Nephew along with the reasons for the departure, including relationship to the therapeutic use of the device.

VIII. STATISTICAL METHODS

A. Literature Control

For the current investigation, ahistorical control has been determined using the Australian Orthopedic Association National Joint Replacement Registry Annual Report 2009 (See below).

Survival Estimate of Primary Knee Replacement (Annual revision free rate * follow-up interval in years)

	1 year	3 year	5 year	7 year	8 year
Total Knee	**99.0%**	**97.2%**	**96.2%**	**95.4%**	**95.0%**

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For the current study, the revision free rate will be based on knowledge of parametric proportional hazards models. The survival times with an exponential distribution have a constant hazard function associated with exponential distributed survival time. Thus, for individuals sampled from this exponential survival distribution, the probability of surviving beyond time t=8 years is 0.95. The entire survival distribution can be defined by the same parameter value λ=0.0064 (nQuery Advisor 6.01).

B. Non-inferiority Analysis

As previously reported, an annual survival rate was extrapolated using equivalency of exponentially distributed survival times to determine 10 year survivorship. As such, the current 10-year investigation will utilize a control survival rate of approximately 93.7% (nQuery Advisor 6.01).

All subjects implanted with the LEGION® Primary Knee System, who meet the inclusion and exclusion criteria and who gave their voluntary consent to participate in the study will be included in the analysis. The analysis will include the description of subject demographics and baseline characteristics. Accountability data will include the number of subjects enrolled and the followup data collected. Data will be analyzed separately for changes from preoperative at 3 months, 1 year, 2 years, 3 years, 5 years, 7 years, and 10 years(if required). Safety will be assessed by identifying and summarizing device-related adverse events throughout the study.

The sample size is calculated based on the non-inferiority of the study device; the following hypotheses will be tested to test the difference in cumulative percent survival of the study device with the literature reference rate with a non-inferiority margin, $\delta>0$:

$H_0: \pi_0 - \pi \geq \delta$

$H_a: \pi_0 - \pi < \delta$

Where π is the cumulative percent survival of study device and π_0 is the reference rate, respectively. δ=0.07. For these hypotheses, rejection of the null hypotheses will imply non-inferiority of the study device compared to the reference rate.

For the above hypotheses, the sample size for a specified α and power 100(1 – β)% is given by,

$$n = \frac{(z_\alpha + z_\beta)^2 [\pi (1 - \pi)]}{(\pi_0 - \pi - \delta)^2}$$

(Chow et al, 2003), where δ is the non-inferiority margin and nonnegative number.

The cumulative percent survival for the study device is unknown for this population, but there is no reason to believe that it would be less than the reference rate. Therefore, a conservative success rate of 93.1% for the study device is used at 10 years. The non-inferiority margin δ of 0.07 is chosen in the study (p13, Chow, Shao, and Wang, 2003). 96 subjects are required to achieve 100(1 – β) % =80% power to detect non-inferiority at the Significance level of α = 0.05. Based on the experience study, allowing 30% of the subjects lost to follow up by the end of 10 years, a sample size of at least 138 subjects are needed in this study. Therefore, a total of 138 subjects will be enrolled into the study in up to 8 clinical sites.

C. Statistical Methods

Primary and secondary outcomes will be evaluated with the use of listings and summary statistics. 95% confidence intervals will be calculated for proportions and averages corresponding to the clinically significant outcomes. Improvement in pain and function will be analyzed using t-test or Wilcoxon Rank tests. Kaplan-Meier estimates will be used to analyze the survivorship of the prosthesis. For survivorship analyses, revision will be defined as failure. Adjustment of prognostic factors to the improvement in outcomes will be performed if needed using appropriate parametric or non-parametric statistical analysis. All statistical analyses and calculation of confidence intervals will be performed using SAS or other appropriate statistical software. An alpha value of α=0.05 will be used in all hypothesis testing.
Experience from numerous studies has revealed that most of the missing data are usually due to lost to follow-up, revision, death and subject withdrawal. A complete accountability along with the explanation for lost-to-follow-up, death, revision, and withdrawn subjects will be provided in the final study report. The missing due to revision will be treated as device failure. A complete assessment of the informative/non-informative missing data will be performed using Kaplan-Meier (KM) method. The KM estimate of the success rate along with the 95% confidence interval of the estimate will be included in the final report.

IX. STUDY SUPERVISION

A. Investigator Responsibilities

The investigator is responsible for ensuring that the investigation is conducted according to the Statement of Investigator, this Protocol and applicable FDA regulations as required. Investigator responsibilities are defined in Title 21 of the US Code of Federal Regulations Part 812, Subpart E and in ICH GCP guidelines.

B. Sponsor Responsibilities

Designated qualified personnel from the Clinical Affairs Departments at Smith & Nephew have been designated for study management and study monitoring. Smith & Nephew reserves the right to contract with qualified clinical research consultant(s) to manage the study and/or perform administrative duties.

Responsibilities of the study manager include:

- conducting site qualification visits (if applicable);
- receiving completed case report forms;
- monitoring the study to ensure that proper records are being kept, study procedures are being followed; and complete and accurate data are being collected

For any questions regarding this study, please utilize the following study contact information:

Study Manager:	Cathy Newbill, CCRA Sr. Clinical Affairs Specialist 7135 Goodlett Farms Parkway Cordova, TN 38016 Tele: (901) 399-6422 FAX: (901) 399-1696 Email: cathy.newbill@smith-nephew.com
Secondary Sponsor Contact:	Jason G. Jones, MS, CCRP Group Director, Clinical Affairs Manager 7135 Goodlett Farms Parkway Cordova, TN 38016 Tele: (901) 399-5583 FAX: (901) 399-1696 Email: jason.jones@smith-nephew.com

A site qualification visit may be conducted before the study is initiated. Close contact will be maintained between the study manager and the investigational site to ensure that data regarding each subject is expeditiously sent to the Sponsor for review. The adequacy of the facilities, the availability of the investigator, the potential number of study participants, and the provisions for support staff will also be assessed during any site visit.

To ensure that the investigators and his/her staff understand and accept their defined responsibilities, the monitor or their representative will maintain regular correspondence and may perform periodic site visits during the course of the study to verify the continued acceptability of the facilities, compliance with the protocol, and the maintenance of complete records. Monitoring will include review and resolution of missing or inconsistent data. The Sponsor currently uses the Chief Medical Officer as a Medical Advisor to advise on medical issues related to clinical studies (contact information for the Medical Advisor can be found on page 2).

X. IRB/IEC & INFORMED CONSENT REQUIREMENTS

Investigators are responsible for obtaining approval from the appropriate IRB/IEC committee prior to study initiation. A copy of IRB/IEC approval documents should be forwarded to the study manager at Smith & Nephew. The local hospital's IRB/IEC committee should give this approval, or should provide a waiver document for the investigator to use a central IRB/IEC. Typically the IRB/IEC approval consists of the protocol, the informed consent form, recruitment materials, and often the case report forms and associated documentation. A copy of the IRB/IEC approval documentation must be provided to sponsor prior to initiation of site, and receipt of subject study binders.

As institutions vary, so do the requirements regarding medical device studies and the subject informed consent requirements. It is the Investigator's responsibility to ensure that appropriate ethical oversight is obtained. Both the investigator and the Sponsor are responsible for ensuring that the study is conducted in compliance with the approved study protocol, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements. The Investigator is required to report withdrawal of IRB approval to Smith & Nephew within five days.

XI. DISCLOSURE OF DATA AND DATA-SECURITY

A. Disclosure

Individual investigators may request summaries of their subject data by contacting the clinical study manager. However, if review of another Investigator's data is requested for comparison purposes, the study manager must have confirmation of the involved Investigator's authorization before release of their data can occur. Entire study summaries can be provided without such authorization(s), but the summary will not be stratified by individual surgeon or obtain surgeon identifiers.

B. Data-Security and Confidentiality

The records of this study will be kept private. In any sort of published report, there will be no identifying information. Records for this study may, however, be reviewed by representatives of the Institutional Review Board, which is the committee that oversees research, the United States Food and Drug Administration or other government agencies, and authorized representatives of the Sponsor or Investigator participating in this study may inspect and photocopy all medical records applicable to involvement in this study. To that extent, confidentiality is not absolute.

Surgeons will notify subjects as to any new information during the course of the study which may affect continued participation.

Participating subjects will be asked to sign a consent form. It allows the study Sponsor and the study investigator to collect, process and pass on to the Sponsor organizations any relevant personal de-identified health information collected from the subject, including billing records, during the study. These are activities routinely carried out during all clinical studies. If the subject decides to take part in the study, and the Investigator cannot locate the subject, the site will attempt to make contact using all reasonable methods including use of Private Investigative services. The Private Investigator would only be given subject name, address, phone number, and date of birth as a means of location.

De-identified personal information (including sensitive personal health information, such as medical history and racial / ethnic origin if relevant to the study) will be reviewed, collected on a computer database, stored in electronic or manual files, audited, and / or otherwise processed by:

- the clinical study investigator and his associates
- the study sponsor, Smith & Nephew, and / or its associate companies
- regulatory or other governmental authorities of the United States and other countries
- other persons authorized by the study sponsor
- the investigator's employees
- Other persons or agencies as required by law or allowed by federal regulations

Personal data will be collected and processed to:

- check suitability to take part in the study
- monitor treatment with the study device
- compare and pool treatment results with those of other subjects in clinical studies
- support the development of the study device

- support the licensing application for regulatory approval of the study device in the world
- support the marketing, distribution, sale and use of the study device anywhere in the world

Personal information may be processed within the US or elsewhere in the world. The Sponsor, an associated company, or a carefully selected third party organization may transfer, process, store, or review personal information inside, or outside, the US. Subjects are free to refuse authorization to transfer personal information. If the subject chooses not to agree to this authorization, the subject may be ineligible to participate in the study. If the subject chooses not to sign the authorization, it will not harm relations with the surgeon.

The subject has the right to inspect their medical records at any time. Research records may be unavailable until the conclusion of the study. At that point, it will be made available. The subject may speak with the surgeon in order to access records.

Whenever personal information is processed; it will be kept confidential and secure to the best of the Sponsor and Investigators ability. It will be used only for the purpose for which it was collected.

Retention of Records – The Investigator and Sponsor are required to maintain all study documentation for at least 3-5 years after the conclusion of the study. Thereafter, written permission is required from the study monitor in order to move or destroy any study document. If subjects wish to revoke authorization to use personal information, the subject shall inform their surgeon in writing. Also, even after participation in the study ends, the Investigators and Sponsor may continue to use and disclose the de-identified health information obtained during the study, before the end of study participation.

C. Use of Information and Publication

Should the investigator wish to publish the results of this clinical investigation or the results of the activities in this clinical trial, the manuscript shall be submitted to Smith & Nephew for review prior to submitting the manuscript for publication.

D. Subject Drop-out/Withdrawal

Subjects may withdraw at any point during the study. A final evaluation will be completed for all subjects who do not finish the study, and the reason for the withdrawal will be documented. After withdrawing from the study, no effort will be made to follow the subject. The Investigator will sign an End of Study/Exit case report form stating the reason the subject withdrew from the study. However, some actively enrolled subjects will not return for follow-up exams due to a variety of reasons.

Often, actively enrolled subjects move during the course of the study without informing the study site. The investigator/study site is committed to use every reasonable measure to obtain follow-up clinical data. The Sponsor reimburses sites for data collection activities associated with subject clinic follow-up. The Sponsor reimburses reasonable examination and x-ray fees if not covered by subject's insurance or are otherwise considered non-standard practice at a clinic or institution. Due to the long length of the study, sites will attempt to contact still active but non-respondent subjects using phone calls, regular mail, e-mail, certified letters or other means to urge subjects to return for clinic follow-up or ascertain if a subject has moved, died, or otherwise become lost to follow-up. These actions, along with any other options available to the site, should be followed to exhaust all reasonable means in locating lost subjects. These actions should be documented in the subject's records and may be performed concurrently or in parallel.

XII. COMPLETION OF STUDY

The Investigator is expected to complete enrollment and follow up per the clinical trial agreement. Continuation of this study beyond the agreement must be mutually agreed upon in writing both by the investigator and by the sponsor. It is agreed that either the investigator or the sponsor, may terminate this study before the above date, provided a written notice is submitted at a reasonable time in advance of intended termination. After conclusion of the study, the sponsor will prepare a clinical summary which will include tabulations of the data used to evaluate safely and efficacy.

XIII. INVESTIGATOR AGREEMENT

A fully-executed Statement of Investigator that includes the investigator and co-investigators, must be in place prior to any study-related activities occurring.

XIV. REFERENCES

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