Prospective Multicenter Post Approval Study of the LPS-Flex Mobile Bearing Knee

Protocol # 07-100

Clinical Study Protocol

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Zimmer, Inc.
PO Box 708
Warsaw, IN 46581-0708

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1. **Protocol Summary**

The objective of Post Approval Study (PAS) is to assess the long-term performance of the *NexGen*® LPS-Flex Mobile Bearing Knee in the treatment of patients with severe knee pain or degenerative knee disease. The target population of 400 cases will be from two parallel groups.

Group 1 will consist of approximately 300 patients already implanted with either the LPS-Flex Fixed Bearing Knee (control population) or the LPS-Flex Mobile Bearing Knee device during the IDE study from approximately 10 sites. These patients will be involved in long-term follow-up through 10 years.

Group 2 will consist of approximately 100 new patients who are eligible for a total knee replacement, have been chosen to receive the LPS-Flex Mobile Bearing Knee and meet the study eligibility criteria. The clinical and radiographic data collection will be the same for both groups.

The Knee Society Knee Score will be used for both groups to evaluate clinical parameters such as functional ability, level of pain and range of motion. The SF-12 will be used to assess patient's quality of life status. Radiographic views will be obtained at the immediate postoperative interval (A/P view only) and at each post-operative follow-up interval (A/P and lateral views). In addition to the independent radiographic evaluation at each post-operative follow-up interval, patient improvement in Knee Society and SF-12 scores will be characterized as the change in postoperative scores from the preoperative values, and will be summarized at 6 weeks, 6 months and at annual increments up to 5 years for Group 2 and at 5, 6, 8 and 10 years for Group 1.

Adverse events will serve as clinical study endpoints, and will be summarized over the long-term follow-up period (over the 6 year period beginning at 4 years (if applicable) and extending to 10 years from the date of primary knee replacement surgery) for Group 1, and over the first 5 postoperative years for Group 2.

The length of follow up for Group 1 will begin with protocol approval at approximately 4 to 5 years from the date of the primary knee replacement surgery date and will extend through 10 years from the primary surgery date. A number of patients have reached the 4 and/or 5 year post-operative time point during the period between the submission of the PMA and the launching of the post approval study at which time data was not required to be collected per the IDE protocol. If the 4 and/or 5 year data was collected during this period as part of the surgeons standard of care, the patient informed consent will request permission to collect this retrospective data for use in the post approval study. The length of follow-up for Group 2 will extend through 5 years from the date of primary knee replacement surgery.

2. Introduction

Total knee arthroplasty, TKA, is a medical procedure where the entire knee joint is replaced with a prosthetic device. Since the first total condylar implant procedure in 1974,[1] TKA has become a widely accepted orthopaedic procedure. Each year, approximately 478,000 TKR surgeries are performed in the United States for end-stage arthritis of the knee joint.

Major indications of TKA include osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteonecrosis, and other types of inflammatory arthritis.[3] The TKA surgical procedure involves resurfacing the knee joint by removing diseased bone and cartilage on the surface of the femur, tibia, and patella and implanting an artificial device.

Clinical experience has highlighted the need to minimize wear of polyethylene and transmission of contact stresses to biological interfaces in total knee replacement applications.[1,9,21] It has long been recognized that the wear rate of the articulating surfaces is correlated with the contact pressures imposed upon them during movement.[1,21,] It is difficult, however, to increase the congruency of the tibiofemoral articulation surfaces without detrimentally affecting knee kinematics and increasing contact stress transmission to an unacceptable level.[8,13]

In the natural knee joint, incongruency of the opposing surfaces of the femoral condyles and tibial plateau is accommodated by the menisci, which serve to spread the applied load and thus reduce contact pressure. In the case of artificial knee replacements, it is possible to achieve the same effect by allowing one of the bearing surfaces, typically the tibial articulating surface, to move relative to the other. The advantage of allowing the tibial articulating surface, or (meniscal bearing surface), to move, is that it allows the possibility to retain knee conformity while also maintaining a good range of natural movement and thereby reduce contact pressure.

The LPS-Flex Mobile Bearing Knee is designed specifically to optimize congruency between the femoral and tibial articulating surfaces over the entire range of motion, while providing movement of the tibial articular surface to maintain optimal kinematics. Congruency is important over the entire range of motion because the highest contact pressures are often encountered at significant flexion angles when climbing and descending stairs, and rising out of a chair. In the literature, it has been demonstrated that in high flexion, the tibia will have a tendency to rotate up to 25º.[23] The articular surface of the LPS-Flex Mobile Bearing is designed to permit free rotation about the tibial baseplate trunnion up to 25º of internal or external rotation (total possible rotation is 50º). The tibial/femoral conformity is thus maximized throughout the entire range of motion continuum.

The LPS-Flex Mobile Bearing Knee is a meniscal bearing total knee replacement, designed to accommodate posterior cruciate ligament resection. The device is

designed for use with bone cement only for fixation of all components, which include the femoral, tibial and patellar implant devices.

3. Objective

The objective of PAS is to assess the long-term performance of the *NexGen*® LPS-Flex Mobile Bearing Knee in the treatment of patients with severe knee pain or degenerative joint disease, in comparison with the LPS-Flex Fixed Bearing Knee.. Outcome data will be collected to evaluate:

- Pre and post-operative status of affected knee.
- Alleviation of pain in the knee joint
- Restoration of function
- Radiographic findings
- Quality of life
- Revision, removal or secondary surgery;

Procedure-related complication and device-related adverse events.

4. Study Design

This is a prospective, multi-center, parallel group, active and historically controlled post approval study comparing the clinical performance of the LPS-Flex Mobile Bearing Knee with the LPS-Flex Fixed Bearing Knee. Group 1 consists of patients who received either the LPS-Flex Fixed Bearing Knee or the LPS-Flex Mobile Bearing Knee during the active IDE, completed the two arm randomized actively controlled IDE study and has provided written consent to participate in the post approval study. Group 2 patients will be enrolled into a single arm, historically controlled, short- term study (5 years) and will consist of those patients who are eligible to receive the LPS-Flex Mobile Bearing Knee and will have the device implanted by orthopaedic surgeons experienced in primary total knee replacement.

The post approval study will be offered to all Group 1 patients who participated in the IDE portion of the study and agree to participate in the post approval study. For those patients willing to consent to continued follow-up, visits will occur at the following post-operative intervals: Years 5, 6, 8, & 10. All data will be recorded on the Study Case Report Forms (CRFs) which will be provided to each site. As stated in Section 1, if the 4 and/or 5 year data was collected during the period between the submission of the PMA and the launching of the post approval study as part of the surgeons standard of care, a request will be made to the patient in the informed consent requesting permission to collect this retrospective data for use in the post approval study. The retrospective data will include any data collected by the investigator per his/her standard of care. If the data collected includes all data points as specified in the IDE, this information will be transferred onto the post approval case report forms

and reported as part of the post approval study. If the data collected includes any of the data points as specified in the IDE, this information will be transferred onto the post approval case report forms and flagged to be analyzed separate from the study data.

Patients in Group 2 will be selected according to the Patient Eligibility Criteria set out in Section 5. Data on pain, function, deformity, radiographic parameters, and complications will be collected. Patients undergoing primary total knee arthroplasty which require a bilateral procedure will also be eligible for inclusion into Group 2. Follow-up examinations will be made at 6 weeks, 6 months, 1 year, 2 year, 3 year, 4 year, and 5 year intervals.

Up to 5 new sites will contribute subjects to Group 2 of the post approval study of the LPS-Flex Mobile Bearing Knee Prosthesis. Surgeon selection will be based on the following criteria: 1) the surgeon is willing to conduct this research study in accordance to the protocol and applicable federal regulations, 2) the surgeon identifies staff to assist him/her to conduct the research and collect the required data and 3) an adequate patient population exists to support study enrollment requirements. This number of centers will permit assessment of the consistency of outcomes across a variety of investigators. Each site will enroll approximately 20 patients. The enrollment period may be 12 months or longer to assure an adequate number of cases at each site.

4.1 Additional Data Sources

Additional data sources (i.e. Australian Registry) will be requested annually to provide further information on the long term safety and efficacy of the *NexGen* LPS Flex Mobile Bearing Knee, in comparison with the LPS-Flex Fixed Bearing Knee. Please refer to Section 17 for further details regarding the acquisition and use of this data.

5. Patient Selection Criteria/Recruitment Strategy

In order to avoid possible ascertainment bias, the investigator agrees to screen all presenting total knee replacement patients against the patient eligibility and contraindication criteria and to offer enrollment to all consecutive patients (Group 2) that satisfy the criteria. The investigator also agrees to provide an informed consent to these presenting patients, who satisfy the patient eligibility and contraindication criteria as specified below.

Patients must meet the following criteria to be eligible for participation.

5.A. Patient Eligibility Criteria

Enrollment into Group 2 of the PAS will be offered to all patients who present with severe knee pain and disability due to:

- Osteoarthritis (OA)
- Primary and secondary traumatic arthritis
- Avascular necrosis of the femoral condyle
- Moderate varus, valgus, or flexion deformities (i.e. valgus/varus deformity of ≤15˚, fixed flexion deformity of ≤10˚)

5.B. Contraindications

- Contraindications include:
  1. Previous history of infection in the affected joint and/or local/systemic infection that may affect the prosthetic joint.
  2. Insufficient bone stock on femoral or tibial surfaces.
  3. Skeletal immaturity
  4. Neuropathic arthropathy
  5. Osteoporosis or any loss of musculature or neuromuscular disease that compromises the affected limb.
  6. A stable, painless arthrodesis in a satisfactory functional position
  7. Severe instability secondary to the absence of collateral integrity
- Total knee arthroplasty is contraindicated in patients who have rheumatoid arthritis (RA) and an ulcer of the skin or a history of recurrent breakdown of the skin because their risk of postoperative infection is greater. RA patient using steroids may also have increased risk of infection. Late infections in RA patients have been reported 24+ months postoperative.
- Patient is a poor compliance risk, i.e., history of ethanol or drug abuse, or mental handicap that would compromise patient compliance with respect to rehabilitation or follow-up.
- Patient is not willing or able to give informed consent to participate in the follow-up program.
- Patient is not willing to return for all scheduled follow-up appointments as defined by this protocol.

Participation in Group 1 will be offered to all subjects enrolled in the LPS Flex Mobile IDE study. Of the IDE study participants, it is anticipated that approximately 150 procedures implanted with the LPS-Flex Mobile Bearing Knee and approximately 150 procedures implanted with the LPS-Flex Fixed Bearing Knee will be included in this arm of the study. Group 1 subjects are subjects: 1) without preoperative diagnoses of rheumatoid arthritis, 2) implanted with a study device, 3) completed the (IDE) study, 4) will agree to be consented for the post approval study and 5) are willing to be re-evaluated for their ability to comply with the follow-up schedule specific to the post-market approval study. All patients from the IDE study cohort will be followed unless any of the following occurs: 1) refusal to provide informed

consent to participate in the PAS, 2) death, or 3) voluntarily withdrawal from participation.

Group 2 will consist of approximately 100 unilateral procedures which are implanted with the LPS-Flex Mobile Bearing Knee, have signed the informed consent, and are evaluated using the patient eligibility/contraindication criteria specific to the post-market approval study. Group 2 patients will have a shorter period of follow-up, and will be followed until death, revision (or re-revision), withdrawal, or 5 years whichever comes first. All procedures requiring contralateral knee replacement will be placed into an ancillary bilateral study arm, and reported on in a separate summary of bilateral study procedures. All procedures requiring revision surgery will be placed into a revision study arm, and reported on in a separate summary of revision study procedures.

6. Study Procedures

6.A. Inclusion of Patient

For each consecutive patient in Group 2 presenting as a candidate for total knee replacement, the inclusion and contraindication criteria of Section 5 should be reviewed. If all patient selection criteria are satisfied, the patient informed consent process will be completed. No preoperative information can be collected until the patient informed consent has been signed. A preoperative patient questionnaire, health status patient questionnaire, and preoperative clinical evaluation will be obtained for Group 2.

The investigator or designee will discuss with the IDE patients continuing into Group 1 of the post approval study, the importance of returning for follow-up visits at the required intervals. If during this discussion the patient is identified as a poor compliance risk, (i.e., history of ethanol or drug abuse, or mental handicap that would compromise patient compliance with respect to extended follow-up), this patient would be excluded from the study. Patients having a history of drug and/or alcohol abuse or who are mentally handicapped could have the potential to report inaccurate data during the follow-up visits and/or could be considered a high risk for non-compliance which could inadvertently bias the study. For this reason, these patients will be excluded from the study. Any baseline information and clinical results of these excluded patients at the end of the IDE will be provided in the PAS status report. Once the patient is deemed appropriate for continuing into Group 1, the patient informed consent process will be completed. Study information will not be collected until the patient informed consent has been signed.

6.B. Operative Procedures

Details of the surgical procedures for Group 2 will be recorded on the CRFs provided. Surgical procedures for Group 2 will follow the same procedures that were required for the Group 1 patients enrolled into the IDE phase of the study.

All surgical procedures will be performed under aseptic conditions using the procedure specified in the appropriate surgical technique manual.

All LPS-Flex Mobile Bearing Knee components will be implanted using bone cement of the investigators choice. The surgical technique for implantation of the LPS-Flex Mobile Bearing Knee is included in Appendix 6 of the protocol.

Three separate surgical techniques standard and MIS are available for implantation of the LPS-Flex Mobile Bearing Knee, with the choice of technique related to surgeon preference for specific instrumentation. The techniques include intramedullary instrument, epicondylar instrument and *Multi-Reference*™ 4-in-1 Femoral Instrumentation surgical techniques. All of the instruments used to implant this device are currently available for implantation of the *NexGen* Complete Knee Solution device.

The Operative Information form and Surgical Device Information form will be completed for Group 2 at the time of surgery or immediately thereafter. Similarly, the Immediate Postoperative Evaluation form will be completed as soon as possible after the surgery, but prior to the 6 week follow-up visit. The case report forms to be completed at each event and interval can be found in Appendix 1 of the protocol.

6.C. Follow-Up Procedures

Data needed to complete the functional evaluation and the radiographic evaluation will be collected for both groups in the study.

Group 1: Postoperatively at 4 years (if applicable), 5 years (if applicable), 6 years, 8 years and 10 years.

Group 2: Postoperatively at 6 weeks, 6 months, 1 year, 2 years, 3 years , 4 years, and 5 years .

Acceptable windows for follow-up for both groups are as follows: 6 weeks ±2 weeks, 6 months ± 1-month and yearly ± 2 months. There will be a minimum of 5 years of follow-up for each case in Group 2, although some patients may fail to achieve the minimum 5 year follow-up due to death, withdrawal from the study, or identified as lost to follow-up. If provided with a second, LPS-Flex Mobile Bearing Knee bilateral implant, patients will be asked to

complete two patient questionnaires, and data for each knee implanted will be evaluated on separate case report forms. This information will be analyzed separately from patients with unilateral knee replacement. All patient data will be used in the analysis of re-operation rates, pain scores, deformity scores, radiographic indications, and complication rates for as long as the patient is in the study. This will remain true until lost to follow-up, or the study is closed.

Follow-up Intervals	Group	Follow-up Windows	Months Post-op Range
6 weeks	Group 2	± 2 weeks	4 - 8 weeks
6 month	Group 2	± 1 month	5 – 7 months
1 year	Group2	± 2 months	10 – 14 months
2 year	Group 2	± 2 months	22 – 26 months
3 year	Group 2	± 2 months	34 – 38 months
4 year	Group 1 (if applicable) Group 2	± 2 months	46 – 50 months
5 year	Group 1 (if applicable) Group 2	± 2 months	58 – 62 months
6 year	Group 1	± 2 months	70 – 74 months
8 year	Group 1	± 2 months	96 – 98 months
10 year	Group1	± 2 months	118 – 122 months

Radiographs (A/P and lateral views) for Group 1 will be required at each postoperative interval as specified in the protocol. Radiographs for Group 2 will be required at the preoperative interval (A/P and lateral views), at the immediate postoperative interval (A/P view only) and at each postoperative interval (A/P and lateral views) as specified in the protocol. All radiographs (Group 1 and Group 2) will be reviewed by the investigator at each interval and a Radiographic Review Form will be completed. If a significant radiographic event is identified, a Significant Radiographic Event form will be completed. An independent radiographic review will be performed on Group 1 and Group 2 at all PAS post-operative follow-up intervals. (See Section 8B).

7. Plan to minimize Loss to Follow-up

Patient follow-up is extremely important for the conduct of a sound clinical study. The expectation of the FDA is to obtain an 80% follow-up rate by the end of this

study. In an effort to minimize lost to follow-up study subjects, the following recommendations and/or study requirements are essential to ensure proper patient selection and compliance.

All Group 2 patients will be selected according to patient eligibility criteria detailed in Section 5 and are expected to return for all follow-up visits. Patients from both groups will be counseled during the informed consent process on the importance of returning for follow-up visits. Patients who are not willing to return for study required follow-up visits and/or are not willing to comply with the follow-up schedule will be excluded from enrollment in the study. In addition, if a patient is a poor compliance risk, (i.e., history of ethanol or drug abuse, or mental handicap that would compromise patient compliance with respect to extended follow-up) that patient will be excluded from the study. Patients having a history of drug and/or alcohol abuse or who are mentally handicapped could have the potential to report inaccurate data during the follow-up visits and/or could be considered a high risk for non-compliance which could inadvertently bias the study. For this reason, these patients will be excluded from the study. Any baseline information and clinical results of these patients at the end of the IDE will be provided in the PAS status report.

In addition to proper patient selection, patient due notices will be sent to the sites on a regular basis in order to track each study participant and monitor adherence to the required follow-up visit timeframes. The patient due listings will facilitate scheduling the patients for their return office visits. If during the course of the study it is determined that a patient is experiencing a financial hardship that prevents the patient from returning for follow-up visits, Zimmer should be notified to discuss possible financial assistance which may be available to the patient.

Attempts to contact patients will be documented on the Study Completion form. It is recommended that the first three attempts be made by telephone. If a response is not received from the phone calls, a letter from the investigator should be sent to the patient explaining their agreement per the informed consent to comply with the follow-up intervals as stated in the protocol. If a response is not received from this letter to the patient, the final recommendation would be to send a certified letter to the patient. If no response is received from the certified letter, the patient will be deemed lost to follow-up and a study completion form will be completed.

In addition, patient contact information of two additional sources will be requested from the patient and collected on the Confidential Patient Information form. If the patient is unable to be located either by direct contact to the patient or the two additional sources listed on the Confidential Patient Information form, the National Death Index will be used to determine whether the patient has died. If the patient should decide to withdrawal from study participation, the Study Completion form will include documentation for the reason of withdrawal. It will also have a question which requests permission to contact the patient at the end of the study to assess the experience with the device.

Should these recommendations and/or requirements fail to achieve the FDA required 80% follow-up compliance for Group 1 at the 10 year time point, the follow-up requirements for Group 2 will continue until the patients reach the ten year post-operative interval. These patients will be expected to continue annual post-operative follow-up visits at 5, 6, 8 and 10 years. The consent for Group 2 will include the following statement to allow for additional follow-up out to the 10 year time point. *"You will be required to complete follow-up visits at 6 weeks, 6 months, and annually out to 5 years. However, if at the end of the 5 year period, additional data is required to fulfill FDA requirements, you may be asked to continue annual post-operative follow-up visits at year 6, 8, and 10."*

8. Data Collection

8.A. General Instructions

Bilateral cases will require the completion of two separate sets of case report forms (CRFs) and thus will have two separate identification numbers.

The CRFs should be completed in black ink.

Data corrections should be made by striking out the incorrect entry with a single line and initialing and dating the change(s), and the correct response marked alongside.

All questions on the forms should be answered. If the information is not available, the supporting information shall be documented in the general comments section of the CRF. This will help to reduce the number of data queries generated for data that may not be available. Consistent occurrences of missing/incomplete data may prevent thorough and proper analysis of the study data.

8.B. Device Outcome Case Report Forms

Pre-operative Assessment (consisting of five different CRFs – *Demographic Evaluation, Patient Questionnaire, Physical Exam, Knee Assessment and Health Status Questionnaire (SF-12)*) will include demographics, relevant medical & surgical history, diagnosis, clinical evaluation (Knee Society Knee Score) and quality of life evaluation (SF-12)

Operation Details (consisting of three different CRFs – *Operative Information, Surgical Device Information, and Immediate Postoperative Evaluation)* will include procedure and device information, length of stay and details of any perioperative complications.

Group 1 patients will return for follow-up visits at 4 years (if applicable), 5 years (if applicable), 6 years, 8 years and 10 years. Group 2 will return for follow-up visits at 6 weeks, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years. There are three clinical assessment forms (*Patient Questionnaire, Physical Exam and Knee Assessment)*, a Significant Radiographic Event form and an SF12 *(Health Status Questionnaire)* form allocated for each routine follow-up visit, with additional forms as required (i.e., *Independent Radiograph Review*, *Concomitant Medical Events/Complication Report* form, *Protocol Deviation* form, and *Study Completion* form.)

Independent Radiograph Review will be performed on all required post-operative follow-up intervals for both Group 1 and Group 2. The findings of independent radiographic review will be captured on the Independent Radiograph Evaluation form. If the findings of the independent reviewer are different from that of the investigator review, the independent review will be considered the final determination.

Adverse Events/Adverse Device Effects/Complications Reporting will include a description of all complications, onset date, type of event, severity, relation to the device, treatment and outcome. One *Concomitant Medical Events/Complications Report* form is completed for each complication identified during the course of the study.

Study Completion forms will be completed if one of the following events occurs:

1) Patient completes study follow up,
2) Patient withdraws from the study,
3) Patient death,
4) Patient is lost to follow up,
5) The patient undergoes revision of the study implant (or revision implant where warranted), (*Please Note*: these patients will be classified as a failure and moved into the Revision arm of the study) or
6) Other reason such as senility or dementia.

The form will include the date of study completion, study completion status, (e.g. patient expired, lost to follow-up, withdrawal of consent, implant revision, etc.) and questions regarding if the device is still in place and if the patient is experiencing any complications at date of last contact.

Revision Study Subjects

Any study subject who undergoes a revision procedure during the course of this post-approval study will be terminated from their respective group and moved into the revision arm of the study, per request of the FDA.

Revision information will be collected on the Reoperation/Device Removal form and include the following information:

1) Component removed,

2) Reoperation information consisting of reason for removal, date of removal, new components implanted, disposition of device,
3) Re-operative findings, and
4) IRB notification.

The revision surgery information will be collected on the Revision Operative Information form and the Revision Surgical Device Information form which will be completed at the time of surgery, or immediately thereafter. The Revision Immediate Postoperative Evaluation form will be completed as soon as possible after the surgery, but prior to the 6 week follow-up visit. The post-operative follow-up intervals after revision surgery will be at 6 week, 6 month, and annually thereafter until the study has been completed. The case report forms to be completed at each revision event and interval can be found in Appendix 1 of the protocol.

8.C. Data Collection Schedule

Completed Case Report Forms should be sent directly to the Clinical Affairs Department at Zimmer for data entry, validation and analysis. Please see Appendix 2 of the clinical protocol for a detailed data collection matrix.

8.D. Quality Assurance and Control

Study Monitors from the Zimmer Clinical Affairs Department will visit sites on a periodic basis and will require either direct or indirect access to patient records for monitoring purposes.

Study data will be summarized and reported to the participating centers on an annual basis. Confidentiality of individual site data will be strictly maintained.

9. Statistical Procedures

9.A. Analysis Objectives

The statistical analysis has four major objectives:

(1) to evaluate the ability to replicate the short-term efficacy and the safety of the LPS-Flex Mobile Bearing Knee prosthesis observed in the original IDE study population in a prospective cohort which corresponds to its continued use in routine clinical practice (Group 2);
(2) to evaluate the long-term efficacy and the safety of the LPS-Flex Mobile Bearing Knee prosthesis (Group 1);

(3) to evaluate the combined midterm efficacy and safety of the LPS-Flex Mobile Bearing Knee prosthesis from the combination of two prospective sequential cohorts (Group 1 and Group 2); and
(4) to summarize the short-term (e.g., generally less than 5 years) efficacy and safety in the small subcohort of primary TKAs from Group 1 and Group 2 who undergo revisions during the post approval study.

To achieve these objectives, we will evaluate safety and efficacy through:

(1) A comparison of a clinical success endpoint between unilateral primary procedures in the short-term LPS-Flex Mobile Bearing Knee cohort (Group 2) at the 2+ year postoperative clinical assessment with the full unilateral primary IDE LPS-Flex Fixed Bearing Knee representing per-protocol procedures cohort at the 2+ year postoperative clinical assessment;
(2) A comparison of short-term LPS-Flex Mobile Bearing Knee cohort (Group 2) at the 2+ year postoperative clinical assessment with the full unilateral primary IDE LPS-Flex Mobile Bearing Knee representing per-protocol procedures cohort at the 2+ year postoperative clinical assessment.

(3) A comparison of a clinical success endpoint between the primary unilateral LPS-Flex Mobile Bearing Knee and the LPS-Flex Fixed Bearing Knee long-term cohort (Group 1) at the 10+ year postoperative clinical assessment; and
(4) A comparison of clinical success in the mid-term 5+ year postoperative clinical assessment between the combined LPS-Flex Mobile Bearing Knee (Group 1 + Group 2) and the full unilateral primary IDE LPS-Flex Fixed Bearing Knee historical control representing per-protocol procedures cohort which also includes all IDE per-protocol procedures which were not enrolled in Group 1 by carrying their last postoperative clinical assessments forward to 5 years.
Results of one-sided statistical tests will be given in the statistical analysis because it is of interest to know if the patient outcomes with the LPS-Flex Mobile Bearing Knee are not worse than those observed in the LPS-Flex Fixed Bearing Knee. In addition,
(5) Safety and efficacy parameters will be provided for primary TKAs that undergo revision (Group 1 and Group 2) during the post approval study at the time of clinical assessment. Safety and efficacy will be evaluated for each cohort (and their combination at 5+ years) and results will be compared between the LPS-Flex Mobile Bearing Knee and the LPS-Flex Fixed Bearing Knee.

Analyses of clinical success will also be accompanied by sensitivity analyses which will report clinical success rates for subgroups defined by study device:

(1) Investigative site;
(2) Baseline symptoms (Knee Scores);
(3) Subcohort (Group 1, Group 2, and IDE procedures not enrolled in Group 1);
(4) Patient age;
(5) A 5+ Year results restricted to subjects enrolled in Groups 1 and 2 (i.e., without carrying forward results of all IDE subjects that did not enroll in Group 1);
(6) Missing data imputed as failures (regardless of device group);
(7) Missing data imputed as failures for the LPS-Flex Mobile Knee group and successes for the LPS-Flex Fixed Bearing Knee group;
(8) Missing data imputed as successes for the LPS-Flex Mobile Knee group and failures for the LPS-Flex Fixed Bearing Knee group;
(9) Various proportions of missing data imputed as failures (regardless of device).

Sensitivity analyses are intended to assess the consistency of the results with the LPS-Flex Mobile Bearing Knee prosthesis and the LPS-Flex Fixed Bearing Knee under different conditions.

9. B. Variables for Analysis

Variables to be studied include:

1. Baseline Data

a. Age
b. Sex
c. Symptomatic side
d. Diagnosis
e. Medical history
f. Preoperative clinical and functional analysis (Knee Scores)
g. Operative time

2. Follow-up Data

a. Functional analysis (Knee Scores)
b. Radiographic analysis
c. Complications
d. Implant Survival
e. Quality of Life (SF-12)

Surgical procedures followed to 10 years (Group 1) will be evaluated postoperatively at 4 years (if applicable), 5 years (if applicable), 6 years, 8 years, and 10 years. Procedures followed to 5 years (Group 2) will be

evaluated preoperatively, perioperatively, and in follow-up at 6 weeks, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years.

Randomization Scheme

Patients in Group 2 will not be randomized in the post-approval study, but will be required to provide informed consent, meet inclusion criteria, and be free from attributes represented in contraindication criteria for inclusion. Patients in Group 1 were randomized and implanted with a study device prior to the post approval study.

Sample Size Justification

Sample size serves to characterize safety and efficacy through separate assessments which each are measures of clinical success. Success will be assessed from implant survival, as well as, from clinical, functional, radiographic, and safety evaluations.

Success for each clinical endpoint will be evaluated separately for each procedure at key time points. Each procedure which meets all the criteria for clinical success will be classified as a clinical success.

The following are the five (5) criteria for classification of a procedure as a *clinical success*:

- Knee Society assessment score greater than/equal to 70 points
- Knee Society function score greater than/equal to 70 points
- No intended, actual, or planned revision and/or removal of any component of the knee system
- Absence of severe knee related complications
- An absence of subsidence of greater than or equal to 2 millimeters and an absence of both osteolysis and radiolucencies greater than or equal to 2 millimeters as determined by independent radiographic reviewer

If one or more of the above criteria are unmet, the procedure will be classified as a *failure to achieve clinical success*.

Sample size was based on independent Blackwelder[1] test of clinical success proportions for non-inferiority by a comparison of proportions of primary unilateral procedures implanted with the LPS-Flex Mobile Bearing Knee versus unilateral procedures implanted with the LPS-Flex Fixed Bearing Knee. Clinical success at the 5 year postoperative assessment will correspond to assessments made at follow-up visits conducted at the 58 postoperative month or beyond for both device groups. The LPS-Flex Mobile Bearing Knee estimate will be obtained from the combination of clinical results obtained from both Group 1 and Group 2, as well as subjects in the original IDE group that were not enrolled into Group 1. All LPS-Flex Mobile Bearing Knee

procedures that were not enrolled in Group 1 will be included in analysis, and will have their last postoperative clinical assessments carried forward (LOCF) to 5 years. The LPS-Flex Fixed Bearing Knee estimate will be obtained from clinical assessments performed on Group 1, and will include all subjects in the original IDE group that were not enrolled into Group 1. LPS-Flex Fixed Bearing Knee procedures not enrolled into Group 1 will have their last postoperative clinical assessments carried forward (LOCF) to 5 years for completeness. This comparison will therefore consist of all eligible unilateral procedures. The equivalence of clinical success will be tested using a two-group proportion test.

In addition to the comparison of clinical success of all eligible unilateral procedures at the 5 year postoperative assessment, the equivalence of clinical success will be assessed in secondary analyses at each key protocol-specified scheduled postoperative clinical assessments using a two-group proportion test following the article by Blackwelder.[1] Primary unilateral LPS-Flex Mobile Bearing Knee procedures will be compared with the LPS-Flex Fixed Bearing Knee with restriction to Group 1 procedures at 10 years using FOCB (first observation carried backwards). Clinical success will be compared between primary unilateral Group 2 LPS-Flex Mobile procedures at 2 years and the historical rate in primary unilateral LPS-Flex Fixed Bearing Knee procedures obtained in the IDE study at 2 years. Two year comparisons will be performed using FOCB (or LOCF if FOCB unavailable).

The null (H_o) and alternative (H_1) hypotheses for testing equivalence are represented by:

$$H_o: \ P_{\text{LPS-Flex Fixed Bearing}} \geq P_{\text{LPS-Flex Mobile Bearing}} + \delta$$

$$H_1: \ P_{\text{LPS-Flex Fixed Bearing}} < P_{\text{LPS-Flex Mobile Bearing}} + \delta$$

where, $P_{\text{LPS-Flex Mobile Bearing}}$ is the clinical success rate for the LPS-Flex Mobile Bearing Knee, $P_{\text{LPS-Flex Fixed Bearing}}$ is the clinical success rate for the LPS-Flex Fixed Bearing Knee, and δ is the minimum difference of practical interest. The clinical success endpoint is dichotomous in nature and as a result will be evaluated independently by a two-sample t-test which employs a normal approximation to the binomial distribution.

Sample size determination for the comparison of clinical success rates between the LPS-Flex Mobile Bearing Knee and the LPS-Flex Fixed Bearing Knee at 5 years was completed using a one-sided alpha (Type I) error rate of 5%, and was based on the 2 Year clinical success rate reported in the regulatory submission (IDE G000157) for the LPS-Flex Mobile Bearing Knee (67.7%, Volume 11 page 04329). Sample size was computed with consideration of imbalances between the number of procedures implanted with the LPS-Flex Mobile Bearing Knee in Group 1 and Group 2 and the

control implanted with the LPS-Flex Fixed Bearing Knee in Group 1. A 2:1 ratio of the LPS-Flex Mobile Bearing to LPS-Flex Fixed Bearing Knee unilateral procedures was used in the estimation of sample size.

Specifically, Blackwelder's method was modified to allow for imbalances in sample size. The following formula was used for the one-sided two-group proportion test:

$$Sample\ Size\ (n) = \frac{\left[\left(3(\overline{P} * (1-\overline{P}) * (Z_{1-\beta} * Z_{1-\alpha}\right)^2\right]}{2 * (\delta^2)}$$

Where $\frac{P_{experimental} + P_{control}}{2}$ is the average clinical success rates for the LPS-Flex Fixed Bearing Knee ($P_{control}$) and the LPS-Flex Mobile Bearing Knee ($P_{experimental}$) under the alternative hypothesis.

Table 1: Power analyses for the comparison of clinical success rates at 5+ Years in the Post-Approval Study

Primary Endpoint	Type I Error (α)	Difference (δ)	Power (%)	Estimate of Success in control	N LPS-Flex Mobile Knee	N LPS-Flex Fixed Bearing Knee
Clinical Success	0.05	15%	90	67.7%	274	137
Clinical Success	0.05	15%‡	96.7	67.7%	268‡	134‡
Clinical Success	0.05	10%	62.9	67.7%	274	137
Clinical Success	0.05	10%‡	80	67.7%	268‡	134‡

‡ Sample size determined using additional estimates obtained from the LPS-Flex Mobile Bearing Knee IDE study for per-protocol endpoints at 2+ Years follow-up using a modification of the sample size formula provided in Fundamentals of Clinical Trails (Friedman, Furberg, and DeMets, PSG Publishing, 1985, page 90) :

$$N = \frac{\left[\sqrt{(Z_\alpha^2 * 3 * \overline{p}(1-\overline{p}))} + \sqrt{(Z_\beta^2 * [2 * p_0(1-p_0)] + [p_1 * (1-p_1)])}\right]^2}{2 * \delta^2}$$

Where p(bar) represents the average of p_0 the clinical success rate in the LPS-Flex Fixed Bearing Knee, and p_1 the clinical success rate in the LPS-Flex Mobile Bearing Knee,.

The use of the observed clinical success rate in the LPS-Flex Mobile Bearing Knee (69.9%) resulting in an average rate of clinical success of 68.6%, and adjustment of the non-inferiority margin (10%) to accommodate the 2.2% greater rate of clinical success observed in the LPS-Flex Mobile Bearing Knee (i.e., adjusted to 12.2% for the 10% margin and 17.2% for the 15% margin) for sample size estimation..

Based on the modification of Blackwelder's sample size algorithm, a fixed sample size of 137 implants in the LPS-Flex Fixed Bearing Knee and 274 in the combined LPS-Flex Mobile Bearing Knee study groups (Group 1 + Group 2) at the 5 year postoperative assessment has 90% power to detect a difference in clinical success rates of 15% (δ) or greater at a 1-sided alpha (Type I) error level of 0.05, assuming a clinical success rate in the LPS-Flex Fixed Bearing Knee of 69.4 percent. With additional considerations, a sample size of 153 implants in the LPS-Flex Fixed Bearing Knee and the combined LPS-Flex Mobile Bearing Knee study groups (Group 1 + Group 2) also has 80% power to detect a difference in clinical success rates of 10% at a one-sided alpha (Type I) error level of 0.05. Analyses at the 5 year assessment will ensure an adequate number of procedures are available using an imputation of the first assessment beyond 58 months backwards (FOCB). If the 5 year postoperative assessments are unavailable, then the last postoperative clinical assessment will be carried forward (LOCF).

9.C. General Statistical Methods

At study completion, all cases will be evaluated for compliance with the patient selection criteria and follow-up procedures. A case may be dropped from the final analysis for any of the following reasons:

i. Patient is lost to follow-up
ii. Patient withdraws prior to final follow-up
iii. Patient does not meet patient eligibility criteria
iv. One or more components were improperly implanted (i.e., subjects enrolled but not implanted with a study device at primary knee surgery will not be included)
v. Patient did not comply with follow-up procedures

Any cases dropped from the primary analysis will be evaluated and reported separately.

Data tabulation and summarization will be presented to help in the evaluation of the importance differences in clinical success rates. One-sided statistical comparisons will be performed at an alpha (Type I) error level which will not be adjusted (for multiplicity) and will equal to 5 percent in the test of the null hypothesis of non-inferiority. Tests of the primary hypothesis will be carried out by computing the 95% confidence limit for differences in clinical success rates ($P_{experimental} - P_{control}$) between the LPS-Flex Mobile Bearing Knee (experimental) and the LPS-Flex Fixed Bearing Knee (control), and declaring non-inferiority, if the lower bound of the one-sided 95% confidence limit is greater than the non-inferiority margin (-10%) The non-inferiority of the LPS-Flex Mobile Bearing Knee as compared to the LPS-Flex Fixed Bearing Knee will also be assessed at a non-inferiority margin of -10%. Details concerning the specific testing procedures to be used are reported below.

Point estimates of means or rates will be reported for many results. Confidence intervals are used when it is important to evaluate the uncertainty of an estimate or hypothesis test. In particular, a null hypothesis may not be rejected even though it is false, and a confidence interval can then be used to give a range for the plausible size of the undetected difference.

Secondary analyses will be chosen to be appropriate for the scale and distribution of the measures being analyzed: discrete categorical, discrete ordinal, continuous non-Gaussian, and continuous Gaussian.

Most of the measures analyzed are discrete in nature. This includes patient classification measures, such as diagnosis, as well as several components of the symptom, function, and physical examination evaluation. Most of the components of the function and physical examination are ordinal and will be analyzed as ordinal measures.

Comparisons of distributions of dichotomous variables between a subcohort and the historical control will be performed using Fisher's exact test. Comparisons of distributions of polychotomous variables between a subcohort and the historical control will be performed using a likelihood ratio Chi-square test.

Comparisons of distributions of continuous variables between a subcohort and the historical control will be performed by a comparison of averages using Student's t-test. Significance will be inferred at a 2-sided alpha (Type I) error level of 0.05. The assumption of equal study group sample variances will be assessed using an F-test (folded), at an alpha (Type I) error level of 0.05. If the assumption of equal sample variances is unmet, then a non-parametric Wilcoxon rank sum test will be performed, and significance will be inferred at a 2-sided alpha (Type I) error level of 0.05.

9.D. Specific Analyses

Preoperative, baseline, and perioperative characteristics of the subcohort and historical controls will be compared between study device groups. Those factors that are found to significantly differ at an unadjusted alpha (Type I) error level of 0.05 between the two groups will be considered in a secondary adjusted logistic regression analysis of clinical success which accounts for significant demographic, baseline, and perioperative differences through the use of propensity scores. Specifically, baseline and demographic variables will be used to estimate probabilities of study device group assignment, and the probabilities or propensity scores will be used as an adjustment variable in a secondary adjusted logistic regression analysis of clinical success measures. Demographic, baseline, and perioperative characteristics will also be summarized by study device for each cohort (Group 1, Group 2, and IDE procedures not enrolled in Group 2).

Distributions of available outcomes (Knee Society function and assessment, radiographic parameters, etc.) at each scheduled time of clinical assessment in the short-term arm of the study (Group 2) will be compared between primary unilateral LPS-Flex Mobile Bearing Knee procedures and the historical control of primary unilateral LPS-Flex Fixed Bearing Knee at the 6 Week, 6 Month, 1 Year, and 2+ year postoperative assessments, and parameters will also be summarized for Group 2 procedures that undergo revision at each time point. Distributions of available outcomes (Knee Society function and assessment, radiographic parameters, etc.) will be compared between the LPS-Flex Mobile Bearing Knee and the LPS-Flex Fixed Bearing Knee at each scheduled time of clinical assessment (4 year, 5 year, 6 year, 8 year, and 10+ years) for primary unilateral procedures enrolled in the long-term phase of the study (Group 1), and parameters will also be summarized for Group 1 procedures that undergo revision at each time point.

Revision rates for each cohort or historical control will be estimated using the Kaplan-Meier product limit method. The Kaplan-Meier curves will be plotted over the relevant period of follow-up, and the survival curves will be compared using the log rank and Wilcoxon rank sum tests.

Adverse events will be summarized by study device and group as *patient adverse events* (counted once per patient per type) and, separately, as *adverse events* (counted overall). Adverse event rates will be compared between the subcohort and the historical control using Fisher's exact test at a two-sided alpha (Type I) error level of 0.05. In addition, time-course of adverse events summaries will be performed for patient adverse events and adverse events.

10. Management of Intercurrent Events

10.A. Device Failure / Replacement Procedure

Total knee revision procedures, should they be necessary, must be recorded on the *Concomitant Medical Events/Complications Report* and the *Reoperation/Device Removal* CRF. A full explanation of the cause and treatment is needed. The *Study Completion* CRF should also be completed.

The revision patients will be moved into the Revision Arm of the study and follow-up will continue until the study is completed as stated in Section 8b.

Standard total knee replacement and revision methods will be used in the event of a device failure requiring revision of one or more total knee components. Clinical and radiographic information, and a detailed operative report will be gathered on all revision cases.

10.B. Patient Withdrawal

Subjects have the right to withdraw from the study at any time. The reason for the withdrawal will be documented on the *Study Completion* case report form. In the event of withdrawal, investigators should request permission to contact the study subject at the end of study to find out if the patient had a revision or if the device is still in place. This contact will occur at the 10 year follow-up for Group 1 and at the 5 year follow-up for Group 2.

10.C. Modifications to this Protocol

Neither the investigator nor Zimmer will proceed to 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 Zimmer monitor. It will be necessary to obtain FDA and IRB approval prior to implementation of any changes in the protocol that may affect the scientific soundness or the rights, safety, or welfare of the patients involved.

11. Prior to Initiation of the study

- IRB Protocol Approval

  A copy of the Institutional Review Board (IRB) approval containing the protocol version, the IRB meeting date and the provisions for periodic review in compliance with FDA regulations should be submitted to Zimmer.

- Informed Consent

  A copy of the final, date stamped (if applicable) IRB approved Informed Consent form must be submitted to Zimmer. If the IRB requires a document differing from that provided in the investigational plan, a specimen copy of the Informed Consent should be submitted by the investigator to Zimmer for review and approval by Zimmer and if necessary, the FDA. Informed consent must be obtained for each case prior to study enrollment.

- Clinical Investigator Agreement

  A signed Clinical Trial Agreement (CTA) must be submitted to Zimmer. An investigator will not be permitted to participate in this clinical investigation until the CTA is fully executed and received by the Zimmer Clinical Affairs Department.

12. Informed Consent

Patients should be made aware that their data will be included in a computerized database for this study.

Any additional information required about this study should be obtained from the Zimmer Clinical Affairs Study Manager at:

Kim Rowe
1800 West Center Street
Warsaw, Indiana 46580
Tel: 574-372-4843
Fax: 574-372-4710

13. Annual Reporting to the FDA

Zimmer will submit an Interim Study Status Report to the FDA every six months for the first two years of the study and annually thereafter until a Final Study Report has been submitted. These reports will include information required by FDA guidance document entitled: *Procedures for Handling Post-Approval Studies Imposed by PMA Order* dated August 1, 2007 or otherwise directed by the FDA.

14. Completion of Study

The investigator will complete and report the results of the study in satisfactory compliance with the protocol within 6 months of last patient follow-up.

It is agreed that either the investigator or sponsor may terminate this study before the above date, provided a written notice is submitted at a reasonable time in advance of intended termination. Upon receipt of this written notification by either party, it is understood that no additional patients will be entered into the study.

After conclusion of the study, Zimmer will prepare a clinical summary which will include tabulations of the data reported.

15. Device Retrieval

In the event of a revision, all components revised should be returned to Zimmer for analysis. The investigator must notify the study manager prior to the return of any device. There are three types of returned devices: 1) unused; 2) used, non-contaminated (i.e., the outer package has been opened or the seal has been broken, but the device has not been implanted; and 3) used, contaminated (i.e., those which have been implanted in human subjects).

For used, contaminated devices, immerse the implant in 10 percent neutral buffered formalin, label the implant container to identify the investigator, patient, date of removal, and that the implant is from a clinical study case. Properly prepared specimens are to be sent to:

Zimmer, Inc.
Attention: Product Service Department
1777 West Center Street
Boggs Industrial Park
Warsaw, Indiana 46580

Once the analysis is complete, a copy of the report will be maintained in the study subject records by Zimmer Clinical Affairs and a copy will also be sent to the Investigator for his study records.

A summary of all detailed explant reports will be provided to the FDA in the Annual Reports.

16. Retention of Records

Federal law requires that a copy of all correspondence with Zimmer, study monitor's, IRB's, the FDA, or another investigator, and all records which support case reports of this study must be retained in the files of the investigator for a minimum of two years following written notification by Zimmer that the clinical trial has been completed or has been discontinued.

17. Additional Data Source

Purpose

The intent is to utilize data from the Australian Orthopaedic Association National Joint Registry (AOANJRR) external registry data in order to supplement existing internal data submitted as required for the Prospective Multicenter Post Approval Study of the LPS-Flex Mobile Bearing Knee (P060037).

History

On August 12, 2008, the LPS-Flex Mobile Bearing Knee Post Approval Study Protocol was approved and the study launched as a condition of approval for the LPS-Flex Mobile Bearing Knee System.

The post approval study is comprised of two groups: Group 1 was to include approximately 300 patients (both mobile bearing and fixed bearing) who were enrolled in the IDE study and eligible to participate in the post approval study. These patients were to be followed until the completion of 10-year follow-up visits. However, of the original fifteen (15) sites participating in the IDE study, only nine (9) sites agreed to participate in this post approval study, representing 161 mobile and 146 fixed bearing subjects eligible for study participation, or a total of 307 potential study participants from Group 1. As of

10/1/2013, enrollment in Group 1 is 144 subjects (76 fixed bearing, 68 mobile bearing). All sites in Group 1 are in year 10 of follow-up for those participating patients, with all sites completing 10-year follow-up in 2014.

Failure of Group 1 sites to reach the desired compliance rate for Zimmer to meet the conditions of approval for the post approval study may bias the post-approval study results and decrease the statistical precision of the difference between the LPS-Flex Mobile Bearing Knee and the LPS-Flex Fixed Bearing Knee. Data received from the AOANJRR will be used to supplement data being collected in the post-approval study. This supplements Zimmer data to further demonstrate safety, efficacy and a low revision rate for the LPS-Flex Mobile Bearing device in over 4,000 knees.

Group 2 consists of 3 new surgeons who are to enroll a total of 120 patients. These patients are to be implanted with the LPS-Flex Mobile Bearing Knee and followed until the completion of 5-year follow-up. As of 10/1/2013, enrollment in Group 2 is 119 subjects.

Comparison of Data

Objective
Group 1 participation includes 144 patients (76 fixed bearing and 68 mobile bearing) who have consented to participate in the post approval study and have returned for follow-up evaluations. In order to meet the FDA's PAS requirements, external registry data will be used to supplement current clinical data being collected. The supplemental data will be obtained annually from the Australian Orthopaedic Association National Joint Registry (AOANJRR). The AOANJRR collects data on revision procedures and calculates revision rates by device fixation, type of revision and revision diagnosis on the requested brand name product and compares it to all total knees of the same or similar category performed in Australia. The NexGen LPS-Flex Mobile Bearing Knee System was approved for commercial use in Australia on July 18, 2003.

Data Acquisition
On October 1 of each year, Zimmer will request data for the catalog numbers with descriptions (see Appendix D) for ad-hoc reports from the AOANJRR utilizing the required form (See Appendix E) and requesting specific data available (primary diagnosis, gender, reason for revision) for comparison with data collected as part of the post approval study. Only those component combinations approved in the PMA Application P060037 will be analyzed to obtain current survivorship data for submission with the annual report. Fixed Bearing Components cleared in 510(k) K062768 will be reported as well, because these components were used as the Control Group in the original IDE.

The AOANJRR is a Level 1 Registry and as such, endpoints available for data submitted to Sponsor are limited to revision rates. Per policy of AOANJRR, only verified data published in the current year's registry will be released for reporting purposes (i.e. data published as of December 31, 2013 will be reported in the 2014 annual report). Please review Appendix A for a copy of the data collection tool used by the AOANJRR. As

requested by FDA, Sponsor has provided in Appendix B the "Introduction" section from the 2013 Australian Registry detailing how the data is collected, validated and survivorship estimates are calculated. Included in Appendix C is an example of the reports from AOANJRR for both the mobile bearing knee components as well as the fixed bearing knee components.

The expected reports from the AOA NJRR will include the following:

- Revision Rates
- Primary Diagnoses
- Type and Reason for Revision
- Demographic
  - Gender
  - Age (categorical only)

Data Analysis

Due to the manner in which AOANJRR reports and categorizes age in the registry, age comparison cannot be made. Sponsor will compare revision rates, primary diagnoses, types of revisions and gender for mobile bearing subjects obtained from AOANJRR with mobile bearing subjects' data currently collected for the post approval study. The following are the methods Zimmer intends to use to compare results from the PAS group and the AOA NJRR data:

- Revision rates will be presented for each year where the number of cases at risk exceeds fifty (50). The cumulative percent revision at a certain time is the complement (in probability) of the Kaplan-Meier survivorship function at that time, multiplied by 100[1]. The two survival distributions will be statistically compared using the log-rank test. Statistical inference will be inferred at a Type I error rate of 5%.
- Types of revisions will be compared between the LPS Flex Mobile PAS data and the AOANJRR using a Likelihood Ratio Chi-Square test. Statistical inference will be inferred at a Type I error rate of 5%.
- Primary diagnosis will be compared between the LPS Flex Mobile PAS data and the AOANJRR using a Likelihood Ratio Chi-Square test. Statistical inference will be inferred at a Type I error rate of 5%.
- Gender will be compared between the LPS Flex Mobile PAS data and the AOANJRR using the Fishers Exact test. Statistical inference will be inferred at a Type I error rate of 5%. No p-values will be adjusted for multiplicity.

However, data analyses of the AOANJRR data will not be possible due to the restricted access to the registry's raw data.

Indications for use of the LPS-Flex Mobile Bearing and LPS-Flex Fixed Bearing devices are the same for US as well as Australia.

[1] Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. Adelaide:AOA; 2013, pg 5

IRB Protocol Amendment Approval
This amendment will be submitted for review and approval to all Group 1 and Group 2 participating IRB's. A copy of each IRB's approval for this amendment will be submitted to Sponsor.

Informed Consent
Patients enrolled in the post approval study have signed informed consents detailing the study requirements and are aware their data will be included in a computerized database by Sponsor for this study. Since this amendment does not affect data already submitted and reported to Sponsor, nor will this amendment affect patient safety or well-being, subjects will not be required to sign a new consent.

The AOANJRR supplemental data will be included with all Post Approval Study Annual Reports as required by FDA. The Final Study Report will include the AOANJRR data as well as a comparison of the data as described in the Data Analysis Section on page 24 of this amendment.

18. References

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