A RANDOMIZED CLINICAL STUDY TO COMPARE THE SAFETY AND EFFICACY OF THE OXFORD® CEMENTLESS PARTIAL KNEE

PROTOCOL NUMBER (Study ID): ORTHO.CR.US30

PREMARKET INVESTIGATION NUMBER (e.g. IDE): G100123

PROTOCOL VERSION: 7.0

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1.0 INTRODUCTION

The introduction of mobile bearing knees in the late 1970's was intended to address knee rotation about the transverse axis with designs that combined a highly conforming surface and a mobile polyethylene tibial component. The highly conforming surface disperses contact stresses over a greater area, thus potentially reducing wear. At the same time, the mobile polyethylene bearing allows a degree of motion that has the potential to reduce implant to-bone interface stresses. Such stresses have been shown to lead to implant loosening in highly conforming fixed-bearing knee designs. The defining feature of a "mobile bearing knee" is the presence of a moving polyethylene bearing that articulates with both the femoral condyle and the tibial tray.

In the late 1980's and early 1990's, as life-expectancy and knee replacement co-morbidities began to increase, so did the demand for partial knee replacements. In 2004, Biomet was the first company to offer a mobile bearing partial knee system. The Oxford® Cemented Partial Knee System has experienced great clinical success, however, the use of cemented fixation leaves the patients open to cement related problems such as osteolysis. It is believed that the use of a non-cemented or press-fit Oxford® Partial Knee System will be of benefit to patients and the medical community.

1.1 Purpose and Study Objective

The objective of this clinical investigation is to evaluate the safety and effectiveness of the Oxford® Cementless Partial Knee System. The Oxford® Cementless Partial Knee System is intended to help the patients diagnosed with osteoarthritis or avascular necrosis gain mobility and decrease pain. All of the risks common to a conventional joint replacement are possible with this device as certain risks are associated with any invasive procedures. The study is designed to document and compare the clinical and radiographic results of the Oxford® Cementless Partial Knee System to those of the cemented Oxford® Partial Knee System (control treatment).

2.0 STUDY DESIGN

The study is designed as a prospective, multi-center, single-blind, randomized, controlled study.

The study will be conducted over a period of approximately three to five years and will contain 255 investigational and 128 control knees within the Design Two group and 11 knees within the Design One group (see Study Definitions section for descriptions of these groups). All patients must meet the pre-determined eligibility criteria. Patients will be evaluated pre-operatively, and at 6 weeks, 6 months, 1 year, 2 years and annually thereafter until the last patient entered into this study has completed their 2-year evaluation.

2.1 INCLUSION CRITERIA

1. Patients with a pre-operative Knee Society Assessment Score of <70
2. Patients undergoing primary partial knee arthroplasty as unilateral arthroplasty or bilateral arthroplasty, simultaneously or otherwise

3. Patients diagnosed with osteoarthritis or avascular necrosis limited to the medial compartment of the operative knee joint
4. Male or female patients who are at least 21 years of age at the time of surgery
5. Patients with full thickness cartilage loss, with or without bone loss in the medial compartment
6. Patients with functionally intact ACL and PCL
7. Patients who need to obtain relief of pain and/or improved function in their knee
8. Patients with fixed flexion deformity < 15°
9. Patients who are able to follow post operative care instructions
10. Patients who are willing and able to return for scheduled follow-up evaluations
11. Patients in which natural alignment can be restored
12. Patients who have completed a valid, IRB approved Informed Consent Form
13. Patients with child bearing potential who voluntarily agree to prevent pregnancy for 2 years following device implantation

2.2 EXCLUSION CRITERIA

1. Patients with a pre-operative Knee Society Assessment Score of ≥ 70
2. Patients in which the device would be used to revise a failed prosthesis
3. Patients who are less than 21 years of age at the time of surgery
4. Disease or damage to the lateral part of the knee that in the investigator's opinion contraindicates a partial knee replacement
5. Patients diagnosed with rheumatoid arthritis or other forms of inflammatory joint disease
6. Patients diagnosed with a failed upper tibial osteotomy in the operative knee
7. Patients diagnosed with post-traumatic arthritis after tibial plateau fracture
8. Patients who have had a patellectomy
9. Patients with a flexion deformity > 15°
10. Patients with a fixed varus deformity > 15°
11. Patients who have rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram
12. Patients with a fused knee on operative side
13. Patients who have active or suspected infection, local or systemic that, in the opinion of the investigator, may put patients at undue risk.
14. Patient with pre-existing condition(s) that may interfere with the survival of the implant or their outcomes, including:
    a. Sickle Cell Anemia
    b. Lower extremity muscular atrophy
    c. Neuromuscular disease
    d. Vascular insufficiency
    e. Metabolic Disorders which impair bone formation
    f. Paget's Disease
    g. Charcot's Disease
    h. Osteomalacia
    i. Severe Osteoporosis

15. Patients with clinical conditions that may limit follow-up (in the opinion of the investigator) including;
    a. Immuno-compromised conditions (i.e. HIV)
    b. Hepatitis
    c. Tuberculosis
    d. Neoplastic disease such as cancer of the prostate, lung, stomach, cervix, etc.
16. Chronic renal failure
17. Organ transplant (i.e. heart, liver, lung, etc.) recipients
18. Known disease process that in the opinion of the investigator may limit long term (4 year) follow up (i.e. multiple sclerosis, leukemia, lymphoma, etc.)
19. Patients diagnosed with Parkinson's or Alzheimer's Disease
20. Patients who have had an above-knee amputation in the contralateral leg
21. Instability or deformity of the ligaments and/or surrounding soft tissue, which would preclude stability of the prostheses
22. Patients with a known metal allergy
23. Prisoners or, individuals who are known to be abusing drugs or alcohol or are mentally incompetent
24. Patients who have received systemic steroids within the past 6 months or steroid injection into the affected knee within the previous 6 weeks prior to enrollment
25. Patients who are pregnant
26. Patients with severe valgus or varus knees (valgus or varus angulation of more than 20°) where collateral ligament, iliotibial band, or popliteal release is required
27. Patients who refuse to sign the IRB approved Informed Consent Form
28. Participation in an interventional clinical research study procedure, *other than a bilateral knee arthroplasty in this study*, within the past 12 months
29. Patients with a history of osteomyelitis or sepsis of the index knee
30. Patients who require patellar resurfacing
31. Patients who are not skeletally mature
32. Patients who have had a total hip replacement procedure <18 months prior to entering the study
33. Patients who have had a contralateral non-study knee replacement procedure <18 months prior to entering the study
34. Patients who are found intraoperatively to have inadequate bone stock or other conditions that contraindicate a partial knee replacement

NOTE: Patients implanted on the contralateral knee with the investigational or control device as part of their participation in the study are permitted to be enrolled in the study, but will receive a matching device to the original study knee and will not be randomized.

2.3 PATIENT POPULATION

A Design Two study population of 255 investigational knees and 128 control knees undergoing primary partial knee arthroplasty for any of the diagnoses in the Inclusion Criteria will be included in this study. All patients, regardless of sex, race, or geographic location, must fit into the

scope of the eligibility criteria. All patients must sign an Informed Consent to be enrolled into the study.

2.4 INSTITUTIONS

A maximum of 12 investigational sites will enroll patients into the study.

2.5 STUDY DEFINITIONS

Adverse Event (AE): Any untoward medical occurrence in a patient or subject in a clinical investigation. AEs may or may not have a causal relationship with the device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product.

Design One patients: This is the term for the eleven (both control and investigational) patients enrolled in the study before the cementless (Investigational) tibial design was changed to modify the porous coating.

Design Two patients: This is the term for all patients (both control and investigational) enrolled after the cementless (Investigational) tibial design was changed to modify the porous coating.

Discontinuations: Patients who are lost to follow-up, die or formally withdraw (in writing) their consent to additional follow-up.

Failures: In the patient accounting tables, this represents number of subjects who meet the definition of patient failure at the listed window interval.

Missing Data: Patients who refuse to return for follow-up or who cannot be located and therefore do not formally withdraw consent – also described as "lost to follow-up." Sites will be instructed to continue efforts to contact these patients. See ***Missing Data, Sensitivity Analyses and Accountability Tables*** section for more information on how missing data will be handled in the analysis.

Osteolysis: Osteolysis is defined as a progressive radiolucency of >3mm in ***two or more contiguous zones*** not present on 6 week follow up radiographs and/or a bony destructive lesion that is progressive in nature.

Other Interventions: This category includes other surgeries the patient incurs while enrolled in the study that are seemingly unrelated to the implanted device. This would include surgeries such as cholecystectomy, appendectomy, coronary artery bypass surgery, etc.

Removal: A procedure where all of the original system configuration is removed.

Reoperation: Any surgical procedure that does not include removal or revision, for example, drainage of a hematoma at the surgical site.

Revision: A procedure that removes part of the original implant configuration, with or without replacement of the entire component configuration.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death
- Is life-threatening
  - A life-threatening event is one where the patient is in immediate danger of death unless intervention is done. It does not mean that the patient may die at some time in the future from the event or may have died if the event had been more serious or specific.
- Requires in-patient hospitalization or prolongation of existing hospitalization
  - A planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without a serious deterioration in health is not considered to be a serious adverse event.
- Results in persistent or significant disability/incapacity
  - A significant disability is one that causes substantial disruption to the person's normal life and activity.
- Results in a congenital anomaly/birth defect.

Staged Bilateral: Any contralateral study knee replacement performed during the course of the study, but not under the same course of anesthetic

Unanticipated Adverse Device Event (UADE): Unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with this device, which was not previously identified in nature, severity, or degree of incidence in the application of the device or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If the complication is characterized as an "unanticipated adverse device effect," the investigator will submit a detailed report to Sponsor and the reviewing IRB/EC immediately, but in no event later than ten (10) working days after the investigator first learns of the effect, per 21 CFR 812.150(a)(1). Sponsor, in turn, is required to submit a report to the FDA, all reviewing IRB/ECs, and participating investigators within ten (10) working days.

2.6 RANDOMIZATION

Randomization will not occur until the surgical procedure has commenced. Subjects who have met all eligibility criteria, including the presence of adequate bone stock (see Exclusion #34) following an intraoperative assessment, and have signed the IRB-approved informed consent will be randomly assigned to one of two treatment groups. Patients will be randomized using a 2:1 randomization scheme for investigational:control devices. The randomization plan will be produced using SAS v 9.2 for Windows. Sequentially numbered envelopes will be provided to

each study site to implement randomization. See the Statistical Analysis Plan section for a specific description of the randomization scheme.

The sponsor will review the following preoperative eligibility paperwork: Informed Consent, Historical Record and pre-operative Knee Society Assessment score prior to enrollment in the study and approve randomization for a subject. Control and accountability of the investigational device will be managed in accordance with the sponsor's most current procedure for device accountability.

2.7 PATIENT MANAGEMENT

The table that follows, summarizes the electronic case report forms (eCRFs) required during the course of the study. Preoperative eligibility eCRFs (ICF, HX100 and KSS100) must be submitted and approved by Biomet Manufacturing Corporation before release of the study components/loaner set. All other required preoperative eCRFs (Oxford100), must be entered in a timely fashion, but are not required for the release of the loaner set.

All surgery, immediate post-op and follow up eCRFs are to be submitted to the Sponsor via the electronic data capture system within a recommended 2 weeks of the patient's evaluation date.

2.7.1 Schedule of Events Table

Form Name	Form Number	Version	Pre-Op	Surgery	Immediate Post-Op	6 WK	6 MO	1 YR	2 YR	Annual*
Informed Consent	Per IRB		X							
Patient History Form & Record of Medications	HX100	2.0	X							
Patient Operation Forms	OP100 & OP200	2.0		X						
KSS Scoring Form	KSS100	2.0	X			X	X	X	X	X
Oxford Knee Scoring Form	Oxford100	4.0	X			X	X	X	X	X
Patient Satisfaction Questionnaire	SQ100	1.0				X	X	X	X	X
Radiographic Evaluation *(Completed by Independent Radiograph Reviewer)*	XR100	3.0				X	X	X	X	X
Protocol Deviation Form	PD100	2.0	As appropriate							
Adverse Event Form *(Code List Form AE200)*	AE100	4.0	As appropriate							
Study Completion *(also capturing implant removals)*	SC100	1.0	As appropriate							
Adverse Event Determination	AED100	1.0	As appropriate							

2.7.2 Bilateral Patieint Informed Consent

A patient undergoing simultaneous bilateral surgery under continuous anesthetic may sign one consent form. A patient undergoing staged bilateral surgery must sign one consent for each procedure.

* After the 2-year follow-up, patients will continue to be examined clinically and radiographically on an annual basis until all available study patients have been completed the two (2) years or 24 months follow-up evaluation.

2.7.3 PATIENT EVALUATIONS

Each follow-up visit time point will be determined based on the date of surgery. Every effort should be made to bring patients back within the protocol-defined follow-up windows. All study patients are expected to return for clinical and radiographic evaluation at these specific follow-up intervals. The **Table of Follow-up Intervals** (Section 2.7.4) summarizes the schedule for post-operative follow-up time intervals.

2.7.4 TABLE OF FOLLOW-UP INTERVALS

INTERVAL	FOLLOW-UP WINDOW	MONTHS POST-OP RANGE	DAYS POST-OP RANGE
6 week follow-up	± 3 weeks	1-2	21-63
6 month follow-up	± 1 month	5-7	153-214
1 year follow-up	± 2 months	10-14	304-426
2 year follow-up	± 2 months	22-26	669-791
*3 year follow-up	± 2 months	34-38	1035-1157
*4 year follow-up	± 2 months	46-50	1400-1522
*5 year follow-up	± 2 months	58-62	1765-1887

2.8 PROTOCOL DEVIATIONS

Sites are to identify on the PD200 eCRF, any protocol deviations that have occurred during the conduct of the study. Those found during routine monitoring by the Sponsor, will be brought to the Investigator or designee's attention for reporting.

Protocol deviations will be reported for any deviations from the protocol, including, but not limited to: Informed Consent issues, Inclusion/Exclusion criteria, missed follow-up visits, visits outside of window, missing/incomplete case report forms, surgical procedure deviations and missed radiographs.

A subgroup analysis will be performed to determine if there is a significant difference in patient outcome based on the type of protocol deviation.

*After the 2-year follow-up, patients will continue to be examined clinically and radiographically on an annual basis until all available study patients have completed the two (2) years or 24 months follow-up evaluation.

2.9 ADVERSE EVENTS

The sponsor requires all adverse events as defined in Section 2.5, regardless of relationship to the device, are reported to the Sponsor so that an adequate determination of device safety can be made. All Adverse Events shall be reported on the Adverse Event eCRF (AE100) and assigned an Event Code per case report form AE 100.

Non-Serious Adverse Events: regardless of relationship to the investigational/control procedure/device must be recorded on the Adverse Event Form eCRF(AE100).

Serious Adverse Events: regardless of relationship to the investigational/control procedure/device must be reported to the sponsor on the AE/SAE reporting eCRF (AE100). From the information included on the AE100 form and from any other relevant information collected, the investigator and the sponsor/sponsor's agents will determine which SAEs meet the definition of an unanticipated adverse device event.

Unanticipated Adverse Device Event: reports must be sent to the reporting IRB and the sponsor no later than ten (10) days after the date the adverse event was discovered. Determination of a UADE will be made by the Sponsor per the definition in Section 2.5.

2.9.1 INTENSITY OF SYMPTOMS

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

NOTE: The term "severe" refers to the *intensity* of the event and can be used with any event, without regard to whether or not it meets the criteria for being classified as "serious" or "unanticipated". For example, a subject can have a severe headache, but it is not a serious event.

Under all circumstances, the adequate medical treatment of a suspected complication relating to the investigational device is a prime importance to Biomet.

2.9.2 Relation to Device

- **Not Related:**
  There is no possible relationship between the adverse event and the implanted device.
- **Uncertain:**
  It is not known if there is a possible relationship between the adverse event and the device.
- **Probably:**
  There is a reasonable possibility that the adverse event was caused by the device.
- **Definitely:**
  There is no doubt the adverse event is directly related to the device.

2.9.3 Outcome Definitions

The outcome is in relationship to the Medical / Adverse event, not the treatment rendered, if any, for the event.

- **Resolved**
  The outcome of the medical event has been resolved and / or no further treatment is required to treat the reported condition or illness.
- **Tolerated**
  The outcome of the medical event will most likely never be resolved. The patient "tolerates" the illness or condition as a matter of life.
- **Study Withdrawal**
  Due to the medical event / adverse event the patient was withdrawn from the study.
- **Device Removal / Re-operation**
  The outcome indicates the medical event resulted in the removal of the investigational device or required re-operation of the investigational device.
- **Death**
  The outcome indicates the patient death is a direct result of the reported medical/adverse event.

2.9.4. SAE Reporting for End of Study Event

Patients who will no longer be followed as a study participant due to death must be reported to the sponsor. The investigator or designee must complete and submit an Adverse Event eCRF(AE100) as appropriate, as well as the Study Completion eCRF (SC100).

2.9.5 Review and Remediation of Previously Reported Adverse Events

It has been discovered that many reported adverse events are being reported for normal, early (surgery to 6 weeks) post-operative symptomology, i.e. knee pain, swelling, decreased range of motion, incisional pain etc. which is resulting in an abnormally skewed adverse event reporting trend during the early post-operative phase. In order to correct this reporting trend and avoid potential future reporting bias, all adverse events reported to Sponsor prior to July 11, 2016 (date of database conversion from Joint Assist to Oracle) will be re-assessed and evaluated for reporting appropriateness. If a previously reported adverse event is determined to be a reportable Adverse Event as defined in Section 2.5, a

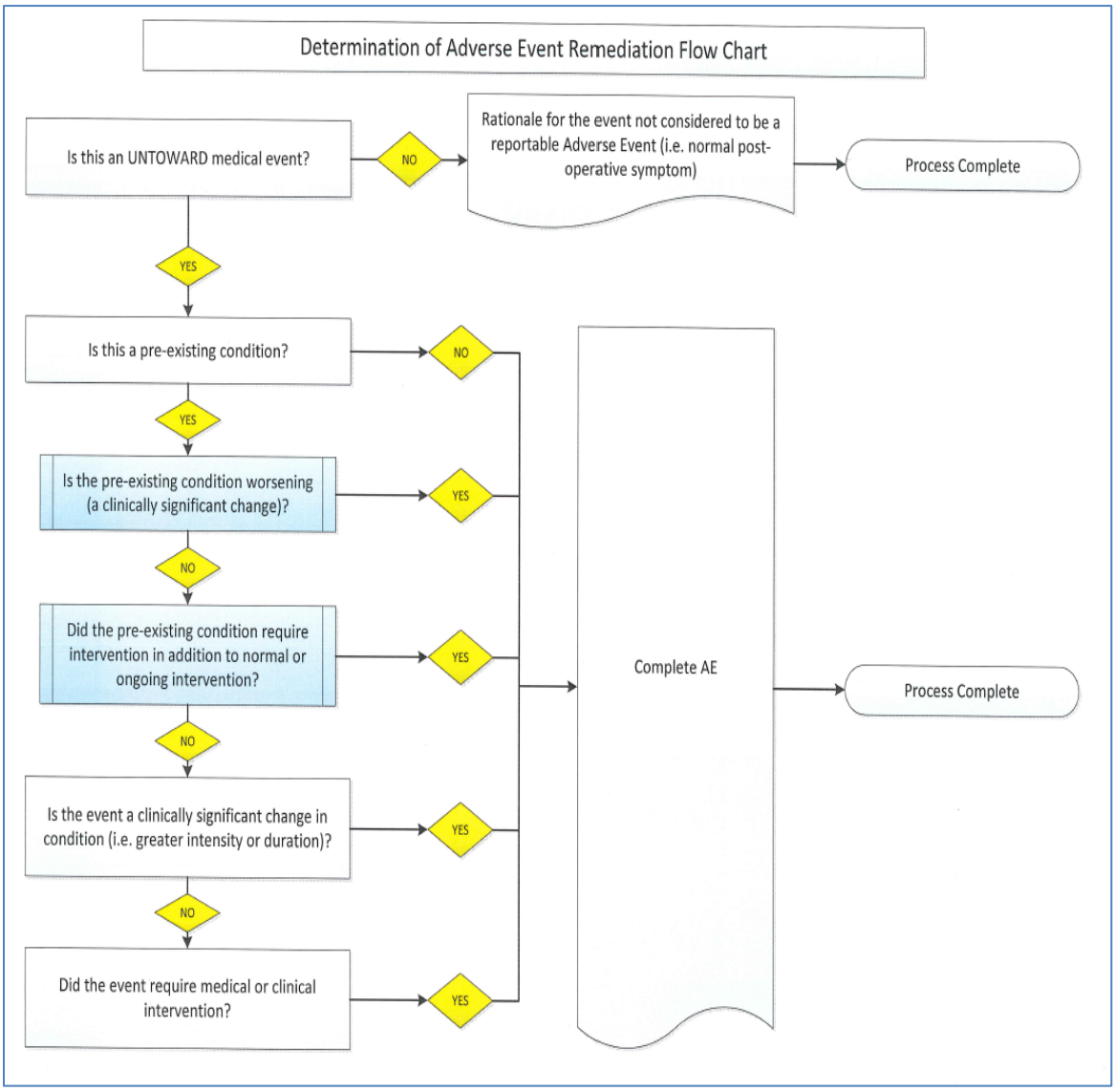
new Adverse Event eCFR (AE100, Version 4) will be completed and submitted to Sponsor. If a previously reported adverse event is determined not to be a reportable Adverse Event as defined in Section 2.5, it will be recorded as "not reportable" in a spreadsheet table and presented in our Annual Reports to the Agency.

A Flow Chart entitled "*Determination of Adverse Event Remediation Flow Chart*" is to be used to determine if a previously reported adverse event will be considered reportable. The sponsor will provide a form entitled "*Adverse Event Remediation: Oxford Cementless IDE*" on every previously reported adverse event as of July 11, 2016 to each site. The remediation form will be pre-populated with the following information:

Header information (Subject ID, Date of Birth (DoB),
Gender,
CRF Completed [date],
Date of Surgery (DoS),
Side,
Visit Date,
Surgeon,
Days since Surgery,
Event Date (Start Date) and
Description of the Event

The pre-populated information will be extracted from the database and entered onto the form "*Adverse Event Remediation: Oxford Cementless IDE*" exactly how it was entered into the Joint Assist database by the site initially. The site will be required to complete each remediation form and the investigator and the site personnel completing the form will be required to sign each form for quality assurance purposes.

2.9.6 Flow Chart for Determination of Adverse Event Remediation



2.9.7 EXAMPLE OF ADVERSE EVENT REMEDIATION FORM

Adverse Event Remediation: Oxford Cementless IDE

Subject ID	«Patient»	DoB	«DoB»	Gender	«Gender»
CRF Completed	«Form_»	DoS	«Surgery_Date»	Side	«Joint_Side»
Visit Date	«Visit_Date»	Surgeon	«Doctor»	Days since surgery	«Days_since_surgery»

Event Date (Start Date)	«Start_Date»
Description of Event	«Description_of_the_adverse_event_»

1. Is this an UNTOWARD medical event?	☐ Yes – Go to Question 3	☐ No – go to Question 2: Not a Reportable Adverse Event
2. Rationale for Not a Reportable Adverse Event*	☐ Normal Post-operative Observation	☐ Other – specify

*** Form is complete if Question 2 is answered**

3. Is this a pre-existing condition?	☐ Yes – go to Question 3a	☐ No – go to Question 4
a. Is the pre-existing condition worsening (a clinically significant change)?	☐ Yes – AE Form Completed **STOP**	☐ No – go to Question 3b
b. Did the pre-existing condition require intervention in addition to normal or ongoing intervention?	☐ Yes – AE Form Completed **STOP**	

4. Is the event a clinically significant change in condition (i.e. greater intensity or duration)?	☐ Yes – AE Form Completed **STOP**	☐ No – go to Question 5
5. Did the event require medical or clinical intervention?	☐ Yes – AE Form Completed **STOP**	☐ No – Complete Question 2

Completed By: _____ Date: _____

Investigator Signature: _____ Date: _____

«Patient» Event Date: «Start_Date» Side: «Joint_Side»

2.10 IMPLANT RETRIEVAL AND ANALYSIS OF REMOVED IMPLANTS

All available retrieved study implants will be handled and analyzed according to the ASTM Standard F-561-97 (current version) and according to the Exponent, Inc. "Oxford Explant Retrieval Protocol" regarding the handling and analyzing of returned explants. Please refer to **Appendix A** for the *Oxford Explant Retrieval Protocol* and information on how and where to return explanted devices.

2.11 PRIMARY AND SECONDARY STUDY ENDPOINTS

The study's primary safety and efficacy endpoints for the Oxford® Cementless Partial Knee System will include:

- Radiographic Success at 22+ months

- Absence of Revision/Removal/UADE at any time point
- The Knee Society Assessment Score at 22+ months
- The Knee Society Function Score at 22+ months

The study's secondary endpoints include:

- The Knee Society Assessment Score at all time points other than 22+ months
- The Knee Society Assessment Score for bilateral subjects at all time points
- The Knee Society Function Score at all time points other than 22+ months
- The Knee Society Function Score for bilateral subjects at all time points
- The Oxford Knee Score at all time points
- Radiographic Success at all other time points
- Single question assessment of patient satisfaction at all time points[a]

The safety of the system will further be monitored by recording and reporting adverse events [including serious adverse events not considered UADEs throughout the follow-up period].

Safety data will be summarized as follows:

- Device removals or revisions
- Unanticipated adverse device events
- Systemic adverse events
- Local adverse events
- Reoperations and Other Interventions

Any patient who fails to return for multiple, consecutive, scheduled follow-up visits for any reason other than the criteria listed above will be identified as Missing Data.

2.12 END OF ROUTINE STUDY ASSESSMENT

Discontinuation/Withdrawal and Post-Routine Exploratory Patients will be recorded on a Study Completion eCRF (SC100). This case report form is completed when the patient completes the study according to the protocol or if there is a change to the active participation of a patient in the study. Examples include lost-to-follow-up, death, or subject removal of informed consent.

Patients who have had an UADE or a Revision and/or Removal of any Device Component should be followed for safety and patient outcomes according to the visits indicated in this protocol (if possible), for the duration of the study. These patients are considered Post-Routine Exploratory Patients.

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[a] Robertsson, Otta, et al. *Patient Satisfaction Compared With General Health and Disease-Specific Questionnaires in Knee Arthroplasty Patients*. Journal of Arthroplasty, 2001, pp 476-482.

2.13 ANTICIPATED CHANGES

It is anticipated that during the course of the study, certain changes may become desirable. These changes may include additional sizes of components or changes in instrumentation. All changes to the investigation require prior approval from investigator's Institutional Review Board (IRB) or Ethics Committee (EC) and if necessary, the FDA. Any other deviation from the stated protocol will be considered a deviation to the protocol and will be reported accordingly. Changes made to the protocol that are made to protect the life or physical well-being of a patient are considered Emergency Changes and must be reported to the sponsor within 24 hours and to the FDA within 5 days of the sponsor's knowledge of the event. Emergency changes to the protocol are not expected to occur for this device type.

2.14 RADIOGRAPHIC PROTOCOL

A detailed radiographic protocol is contained in Appendix D.

3.0 STATISTICAL ANALYSIS PLAN

This is a two-group, multi-center, randomized clinical trial to compare Biomet's cemented Oxford® Partial Knee System to another active intervention, the Oxford® Cementless Partial Knee System (abbreviations: Control vs. Cementless). Imbalanced, blocked randomization (2:1, Cementless vs. Control) will be implemented.

Randomization will be per patient. In the event that an intraoperative screen failure occurs post-randomization, randomization will not be reassigned and this patient will not count toward the overall sample size. Randomization will continue with the next subject enrolled as previously described. The randomization plan will be produced using SAS v 9.2 for Windows. Randomization will be by center, and each site will receive separate randomization plans using a predetermined block size that will remain undisclosed to the sites. The randomization assignments will be in the form of envelopes to be opened intra-operatively after the first tibial cut and bone quality is assessed against the eligibility criteria.

The primary study endpoint will consist of four (4) individual co-primary endpoints, including both safety and efficacy measures. The following endpoints are included as individual parts of the primary endpoint:

1. Knee Society Assessment Score – number of points received for the Knee Society Assessment Score at the 22+ month assessment
2. Knee Society Function Score – number of points received for the Function Score at the 22+ month assessment.
3. Revisions or removals of any component of the device or an unanticipated, device-related adverse event (UADE) at any time point. This is a binary endpoint in which a knee is either a "success" or "failure". To obtain a successful result, a knee must reach the 22 + month upper window limit with the device intact and without a component revision/removal or a UADE.
4. Radiographic Assessments at the 22+ month assessment

   This is a binary endpoint in which a knee is either a "success" or "failure". To obtain a successful radiographic endpoint, a knee must meet the following criteria at the 22+ month
   a. Absence of osteolysis
   b. No migration/subsidence of any femoral or tibial component
   c. Absence of fractured component

Conversely, a radiographic failure is defined as follows:

a. Presence of osteolysis defined as a radiolucency that is both progressive and is greater than 3 mm at its maximum interface in ***two or more*** contiguous zones OR a bony destructive lesion that is progressive in nature.
b. Migration/subsidence of any femoral or tibial component defined as a component migration/subsidence of > 3 mm as compared to 6 week radiographs.
c. A component fracture

3.1 STUDY SUCCESS AND TEST OF THE STUDY'S PRIMARY HYPOTHESIS

This study is designed to show that the investigational device (Cementless) is non-inferior to the Control device using four co-primary study endpoints. This will be shown using a closed testing method in which each of the primary endpoints specified above are compared using α=0.05. Study success requires that the Cementless group successfully demonstrate non-inferiority when compared to the Control group for all four of the individual primary endpoints, using the statistical methods described below. Because non-inferiority must be successfully shown for all four endpoints for study success, the type I error rate is preserved at 5% for the entire primary endpoint.[b] The individual non-inferiority hypotheses for each of these four tests are as follows:

3.1.1. RADIOGRAPHIC SUCCESS

The proportion of radiographically successful knees in the Cementless group is non-inferior to the proportion of radiographically successful knees in the Control group using an 8% margin of non-inferiority. The test is based on the upper bound of a one-sided 95% confidence interval for the difference, Control minus Cementless, of proportions of success at 22+ months. A conclusion of non-inferiority is supported if the upper bound of the confidence interval is 0.08 or less. In addition, a Fisher's Exact p-value will also be computed to test this hypothesis.

In this analysis, each knee will be considered as a separate case, and unilateral and bilateral subjects will be analyzed together, providing the unilateral and bilateral groups are poolable per sensitivity analyses given in Section 3.1.5[c].

3.1.2. ABSENCE OF REVSION/REMOVAL/UADE

Using a 10% margin of non-inferiority, the proportion of knees who are free of Revision/Removal/UADE during the course of the study in the Cementless group is non-inferior to the proportion of such knees in the Control group. The test is based on the upper bound of a one-sided 95% confidence interval for the difference, Control minus Cementless, of success proportions. A conclusion of non-inferiority is supported if the upper bound of the confidence interval is 0.10 or less. In addition, a Fisher's Exact p-value will also be computed to test this hypothesis.

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[b] Dmitrienko, Alex, et al. *Analysis of Clinical Trials Using SAS.* SAS Publishing, 2005, pp 75-76.

[c] As agreed at FDA pre-submission meeting Q160425 April 13, 2016.

In this analysis, each knee will be considered as a separate case, and unilateral and bilateral subjects will be analyzed together, providing the unilateral and bilateral groups are poolable per sensitivity analyses given in Section 3.1.5[d].

3.1.3. KNEE SOCIETY ASSESSMENT (PAIN) SCORE

The mean Knee Society Assessment score (KSSA) for the Cementless group is non-inferior to the mean KSSA for the Control group using a 6.4-point margin of non-inferiority. This test will be based on the upper bound of a one-sided 95% confidence interval for the difference, Control minus Cementless, of means at 22+ months. A conclusion of non-inferiority is supported if the upper bound of the confidence interval is 6.4 or less.

3.1.4. KNEE SOCIEITY FUNCTION SCORE

The mean Knee Society Function score (KSSF) for the Cementless group is non-inferior to the mean KSSF for the Control group using a 9.2-point margin of non-inferiority. This test will be based on the upper bound of a one-sided 95% confidence interval for the difference, Control minus Cementless, of means at 22+ months. A conclusion of non-inferiority is supported if the upper bound of the confidence interval is 9.2 or less.

3.1.5. SENSITIVITY ANALYSES – UNILATERAL AND BILATERAL KNEES

To address the impact of possible correlation occurring due to including two knees from the same patient, for the two endpoints that will incorporate bilateral knees (Radiographic Success and Absence of Revision/Removal/UADE), additional sensitivity analysis will be conducted in order to address any potential correlation occurring due to including two knees from the same patient. These are to include:

a. An analysis that considers only unilateral subjects.
b. A repeated measures model approach that can account for possible correlation within subjects.
c. An analysis of data at the patient level, in which a patient is considered a "failure" if either knee fails.

3.2. CALCULATION OF THE PRIMARY STUDY ENDPOINT

The confidence intervals used in the analysis of the binary primary endpoints (Radiographic Success and Absence of Revision/UADE) will be 1-sided, 95% confidence intervals for the difference between proportions in two independent samples. They will be calculated using the Wald method as based on a normal approximation to the binomial, as follows:

$$(p_C - p_I) + z_\alpha \sqrt{SE_C^2 + SE_I^2}$$

Where

[d] As agreed at FDA pre-submission meeting **Q160425** April 13, 2016.

p_C = proportion of success in the Control group,

p_I = proportion of success in the Investigational group,

α = 0.05, and

$$SE_C = \sqrt{\frac{p_C(1-p_C)}{n_C}} \quad \text{and} \quad SE_I = \sqrt{\frac{p_I(1-p_I)}{n_I}}$$

The confidence interval used in the analysis of the continuous primary endpoints (Knee Society Function and Assessment Scores) will be 95% confidence intervals for the difference between means in two independent samples. They will be calculated using the normal distribution, as follows:

$$(\bar{x}_C - \bar{x}_I) + z_\alpha \sqrt{\frac{s_C^2}{n_C} + \frac{s_I^2}{n_I}}$$

Where

$\overline{x_C}$ = proportion of success in the Control group,

$\overline{x_I}$ = proportion of success in the Investigational group,

s_C = standard deviation for the Control group,

s_I = standard deviation for the Investigational group,

and

α = 0.05

3.3 SAMPLE SIZE JUSTIFICATION

In order to calculate the sample size for this study, the sample size needed to obtain 90% power for each primary endpoint was calculated. The endpoint requiring the largest sample size to maintain 90% power was Radiographic Success. Therefore, this is the sample size used in this study to ensure that we have a sufficient number of knees/patients to test each of the four primary endpoints with at least 90% power.

The sample size for the radiographic success primary endpoint was calculated as follows:

Let p_I and p_C denote the true population proportions of a successful outcome in the Cementless and Control groups, respectively.

Under H_0, p_C is markedly larger than p_I and the Cementless device is inferior. Contrarily, under H_1, this is not true and the true proportion of success for the Cementless device is, at worst, δ less than for the Control. We have $\delta = 0.08$ (i.e., 8%).

Information about plausible values of the proportions p_I and p_C is available in the SSED for the LPS Flex Mobile Device (PMA #P060037). This document was used to help estimate the percentage of radiographic success for sample size purposes because it used a similar radiographic success/failure endpoint as the one given in this protocol. For purposes of the sample size calculation, we use the radiographic failure rates in Table 5 (page 18-19) of the document. This shows a 1.2% radiographic failure rate for the investigational device and a 2.4% radiographic failure rate for the control. Since we have slightly different radiographic success criteria, and because we want to ensure that we have adequate power for testing this endpoint, we will use 5% as our estimate of radiographic failure, giving a 95% estimate of radiographic success.

Assuming 95% to be the true, equal values of p_1 and p_2, non-inferiority sample size calculations were implemented in nQuery Advisor 7.0 software using a 2:1 ratio of Cementless to Control subjects. This software uses methodology as described in an article by Farrington and Manning[e].

Definitions:

p_I: Proportion of successes in the Experimental (Oxford Cementless) treatment group.

p_C: Proportion of success in the Control (Oxford Cemented) treatment group.

For a specified constant, $0 < \delta < 1$, the hypotheses of non-inferiority are:

$$H_0: p_C - p_I > \delta \text{ vs. } H_1: p_C - p_I \leq \delta.$$

Type I error: conclude that the difference p_C-p_I is less than δ when in fact the difference is greater than or equal to δ, *i.e.* conclude that the experimental treatment is non-inferior to the control treatment when the control treatment is actually substantially better.

[e]Farrington and Manning

"Test statistics and sample size formulae for comparative binomial trials with null hypotheses of non-zero risk difference for non-unity relative risk".

Statistics in Medicine 9(1990) pp 1447-1454.

Type II error: conclude that the difference is greater than or equal to δ when it is actually less than δ, *i.e.,* conclude that the experimental treatment is inferior to the control treatment when the experimental treatment is essentially just as good.

Assumptions:

$\alpha = 0.05$	Probability of Type I error
$\beta = 0.90$	Probability of Type II error: power = $1 - \beta$
$p_C - p_I = 0.95$	Estimated success rate for control and treatment groups
$\delta = 0.08$	Non-inferiority Margin

Resulting sample sizes (number of knees), not adjusted for attrition, are 191 Cementless device vs. 96 Control (5% type I error rate, 90% power). We increase our sample size by 10% to allow for possible exclusions in the primary analysis due to bilateral patients who may not be poolable with the unilateral cases, as well as attrition of up to 15%. This gives a sample size of 383 total subjects (255 Cementless vs. 128 Control).

3.4 ADDITIONAL STUDY POPULATION INFORMATION

3.4.1. PER PROTOCOL (PP) POPULATION

Patients who have complete data (i.e. at radiographic, clinical, and safety) collected per the protocol are the Per Protocol (PP) population. Those cases with complete data for a primary endpoint collected per the protocol at 22+ months or who have had a revision/UADE at or before the 22+ month visit will be used in the analysis of that primary endpoint.

3.4.2. INTENT TO TREAT (ITT) POPULATION

Patients who have met the Inclusion/Exclusion criteria, signed the Informed Consent, and been randomized comprise the ITT population and will be tracked. Those patients that have "fallen out" of the study and did not receive either the investigational or the control device will be summarized by specific reason for not receiving the study device. The primary endpoint will be analyzed for the ITT Population as a sensitivity analysis, with the purpose of evaluating the impact of protocol deviations and missing data on the primary endpoints.

3.4.3. DESIGN ONE PATIENTS

All subjects enrolled in the Design One phase of the IDE will be included in this study group. Where sufficient sample size exists, analysis of all study endpoints will be carried out as described in this plan. However, because the investigational devices in this group have a slightly different design and the patients were randomized under a different plan, the group will be analyzed separately from the Per Protocol and Intent to Treat populations (Design Two Patients).

3.5 ANALYSIS OF STUDY DATA

3.5.1. DESCRIPTIVE STATISITICS INCLUSING PATIENTS' BASELINE STATUS

Subjects in the Cementless and Control groups will be compared regarding a list of baseline items, including Knee Society Assessment and Function Scores, demographics (age, gender), medical history, unilateral vs. bilateral status, and use of pain medication for knee-related and non-knee related issues. Standard statistical tests (chi-square, Cochran-Mantel-Haenszel chi-square, Student's t) will be used.

Equitable numbers of men and women are expected to be enrolled. Therefore, we will not perform a stratified analysis for the primary endpoint or stratify randomization on this variable. However, the proportions of males and females in each group will be summarized and compared as stated above in the analysis of baseline data. In addition, the effect of gender on the primary outcomes at 24 months will be assessed within either a linear regression (for continuous primary endpoints) or logistic regression model (for binary primary endpoints) as described below in the Exploratory Analysis section.

Because this is a randomized study, baseline characteristics are expected to be similar between the two treatment groups. If this is not the case based on statistical tests conducted above, then sensitivity analyses will be conducted to assess the impact of the baseline variable in question on study success. In addition, the effect of the baseline variable in question will be assessed within a linear or logistic regression model as described below in the Exploratory Analysis section.

Baseline characteristics will be examined by center in order to determine if there is any center-to-center heterogeneity. Sites with less than or equal to 5 cases in either treatment arm will be combined to form a "pooled" site for analysis. For categorical baseline variables with polychotomous outcomes, differences between treatment groups will be compared across strata (site) using the Cochran-Mantel Haenszel (CMH) test. For dichotomous baseline characteristics (e.g., male/female, unilateral/bilateral) the Breslow-Day test for homogeneity of odds ratios will be used to test for site*treatment interaction, with the demographic variable treated as the "response". For continuous baseline variables, a separate analysis of variance (ANOVA) will be performed for each continuous variable to assess site-to-site variability. In this model, the demographic variable is treated as the "response" and the treatment group, site, and interaction are model terms. The F-test for the interaction term will be used to assess site dependencies.

If site-to-site variability is found, the distribution of the variable in question will be examined by site graphically and descriptively. In addition, the effect of site and the baseline variable in question will be assessed within a linear/logistic regression model as described in the Exploratory Analysis section. If necessary, sensitivity analyses will be conducted to determine what effect, if any, this variability has on the primary outcome.

3.5.2. Analyses of Study Population

Analysis for primary and secondary endpoints will use the Per Protocol population, which consists of those cases with complete data for one or more of the primary endpoints collected per the protocol at the 22+ month follow-up visit (or, as described below in the section on Missing Data, at the last or next available visit if the primary endpoint in question is missing at the 24- month visit). The exception to this is the primary endpoint of Absence of Revision/Removal/UADE, which is cumulative; therefore all cases that have failed at or prior to 24 months due to a revision or UADE will be included in the analysis of that primary endpoint. For each primary endpoint, all available data will be used, even if the subject has missing data for one or more of the other endpoints. Since indications and inclusion/exclusion criteria are exactly the same for both device groups, and because randomization is received at the time of surgery, it is expected that few patients will fail to receive the assigned treatment. However, in the event that they do not, the primary analysis will use the device that was actually implanted if it was a study device; if a study device is not received, the patient will not be included in the primary analysis.

Bilateral patients will be used in the primary analysis for the of Radiographic Success and Absence of Revision/Removal/UADE endpoints, but will be analyzed separately for the Knee Society Function and Assessment endpoints. The bilateral patients will not be included in the primary analysis for the Knee Score endpoints, as there is no way to ensure that the knee scores for one knee will not be affected by the other. The sample size has been increased by 10% to allow for this, a percentage based on the bilateral enrollment in the post-approval study for the Oxford™ Menisal Unicompartmental Knee System.

3.5.3. Study Safety

All adverse events will be recorded, described, and compared for Cementless vs. Control groups. Comparisons will use standard statistical tests (chi-square, Fisher's exact). Adverse events resulting in device removal and/or revision and those not requiring device removal and/or revision will be summarized. Device related serious adverse events will be collected and evaluated for differences across the control and experimental population.

3.5.4. Analyses of Secondary Outcomes

These outcomes include the primary study endpoints at times other than two years. In addition, a composite success/failure endpoint consisting of the four primary outcomes will be tested for non-inferiority, Cementless vs. Control, using a non-inferiority margin of 10%. In this composite, the threshold for success for the Knee Society Assessment and Function scores will be 80 points. A composite success outcome requires a successful outcome for all four components.

In addition, at all-time points, implant revisions or removals will be described by Kaplan-Meier time-to-failure curves and compared using log-rank tests. Mean Knee Society Assessment Score, Knee Society Function Score, and Oxford Knee scores will be displayed by time point and compared between treatment groups. Analyses will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of

the measures being analyzed (chi-square, Cochran-Mantel-Haenszel chi-square, Student's t).

Bilateral patients will be analyzed as a separate group for purposes of secondary analyses of Knee scores at each time point as well in the secondary analysis of composite success rates. For other analyses, including radiographic and safety outcomes, bilateral and unilateral patients will be analyzed together.

Secondary outcomes will be analyzed using all patients with available data for the endpoint being analyzed. As with the primary analysis, the secondary analyses will use the device that was actually implanted if it was a study device; if a study device is not received, the patient will not be included in the secondary analyses.

3.5.5. Missing Data, Sensitivity Analyses and Accountability Tables

Data will be considered "missing" for a given primary endpoint if this endpoint cannot be calculated or is not available for a subject. If the subject has had a device failure or a UADE at any point or prior to their 22+ month outcome, they will *not* be considered as missing data for the Absence of Revision/Removal/UADE endpoint, as this endpoint is cumulative. A subject who has had a revision prior to two years will be considered a radiographic failure at the two – year time point for purposes of the primary analysis. When possible (i.e. the subject is seen by a study investigator in a non-emergency situation and collection of the data will not cause undue burden), Knee Society Scores will be collected for these subjects before the revision is performed in order to prevent these patients from missing knee scores in the primary efficacy analyses. A "worst case" score of twelve will be given for any Knee Scores that cannot be collected prior to the revision procedure.
As an attempt to minimize missing data from the remaining primary endpoints, a next-observation-carried-backward approach will be used to impute values for subjects missing data. Under this approach, if a primary endpoint is missing at the 24 month visit, the subject's next observation post 24-months will be used to impute a 22+ month outcome for that subject, for that particular endpoint. If no data is available after 2 years to carry backward for the missing data point, the subject's latest observation pre-24-months will be carried forward to impute values for the missing 24 month visit.

Sensitivity analyses will examine the sensitivity of the results to missing values of the primary outcomes using a tipping point analysis, a best-case analysis, a worst-case analysis, and an analysis that imputes missing data with the last observation carried forward. If sensitivity analyses do not agree and we have more than 15% of values missing in either group, the method of Multiple Imputation may be used to further investigate the sensitivity of results to the missing data.

Accountability tables will be generated to show, at each study visit, the number of subjects who might be expected to attend a given visit and the number and proportion who did attend. Rows of the table will show counts for subjects contributing all data needed to

create the primary, binary composite outcome and subjects contributing only some of the components of that outcome.

3.5.6. Exploratory Analyses of the Primary Outcome inclusing Center Effects

The association between each primary endpoint and device group at 22+ months across sites will be examined using either an analysis of variance (continuous endpoint) or the Breslow-Day test for homogeneity of odds ratios (binomial endpoint). Sites with less than or equal to 5 cases in either treatment will be combined to form a "pooled" site for analysis. A significant p-value indicates heterogeneity of odds ratios of clinical success across sites, and in this case the proportions of success for each site will be examined graphically and descriptively to assess site dependency.

In addition, the association between device group and each primary endpoint for unilateral and bilateral subjects will be examined using either an analysis of variance or the Breslow-Day test for homogeneity of odds ratios. The test for center effects will use a p-value of 0.05. If there is no evidence of treatment*center interaction ($p \geq 0.05$), data will be pooled across centers. However, the existence of a quantitative interaction between treatment and center does not necessarily invalidate the analysis in pooling data across centers[f]. Thus, if $p < 0.05$ then the observed proportions for each site will be examined graphically to assess site dependency as well as whether or not a qualitative interaction exists. Further, the sites contributing to this interaction will be examined, and if necessary, a stratified analysis will be conducted and results compared to overall study results to assess consistency.

Patient covariates in the proposed statistical modeling below include age at time of surgery, gender, primary diagnosis, unilateral vs. bilateral status, preoperative Knee Society Assessment Scores, Knee Society Function Scores, use of pain medications and study site. Others may be added if other covariates potentially affecting the outcome are observed. To determine the effect of these covariates on the primary endpoints, separate regression models will be used. In the regression models, the dependent variable will be the primary study endpoint; thus a logistic regression model will be needed for the binary study endpoints. The model will also include device group (control or experimental) as an independent variable and the above baseline and demographic variables listed above as covariates. A graphical examination of the residuals will be performed to assess the model assumptions. To determine whether a covariate has an effect on the primary study outcomes, a Type 3 analysis of effects based on the Wald Chi-square test will be conducted.

[f] Gail, M.H., and Simon, R. "Testing for qualitative interactions between treatment effects and patient subsets." *Biometrics*, 1985, **41,** 361-272,

4.0 RISK ANALYSIS

This investigation is designed to collect data on a new mobile bearing partial knee system. The Oxford® Cementless Partial Knee System is intended to help the patient gain mobility and decrease pain. Risks associated with this knee system include general surgical and partial knee arthroplasty risks. Due to the investigational nature of the system, there may be risks that are unknown.

4.1. GENERAL RISKS ASSOCIATED WITH SURGERY

As with any surgical procedure, there are risks involved with partial joint replacement surgery. Potential adverse events include, but are not limited to:

1. Complications resulting from anesthetic
2. Damage to nerves and blood vessels
3. Allergic reactions to the metallic devices
4. Phlebitis
5. Long-term swelling
6. Pulmonary embolus
7. Delayed wound healing
8. Prolonged illness
9. Hematoma
10. Wound dehiscence and/or drainage
11. Excessive bleeding that may result in the need for blood transfusions and/or further surgery
12. Permanent pain, deformity; and inconvenience.
13. Permanent Brain Damage
14. Pneumonia
15. Venous Thrombosis
16. Heart Attack
17. Kidney Failure

4.2. GENERAL RISKS ASSOCIATED PARTIAL KNEE REPLACEMENT

1. Early or late infection perhaps necessitating device removal
2. Component dislocation
3. Fracture or perforation of the bone or device (intraoperative or post-operative)
4. Device loosening or migration
5. Valgus/Varus deformity
6. Inadequate lubrication
7. Patellar tendon rupture and ligamentous laxity
8. Fretting or corrosion of implant interfaces
9. Wear and/or deformation of articulating surfaces
10. Particulate wear debris may initiate a cellular response leading to osteolysis
11. Damage to surrounding tissues, cartilage, or tendons
12. Inadequate range of motion
13. Persistent pain

14. Progression of the disease in the lateral compartment necessitating revision
15. Transient peroneal palsy secondary to surgical manipulation and increased joint movement
16. Implantation of the device may require greater surgical exposure and prolonged surgical time
17. Instability
18. Peripheral neuropathies, heterotopic bone formation and/or histological reactions which may occur with or without clinical significance
19. Failure of cement fixation resulting in loosening of the implant

Rarely some adverse events may be fatal. These possible adverse events are not unique to the Oxford® Cementless Knee System and, as stated above, may occur with any partial joint replacement surgery.

Limitations may be imposed depending upon the patient's age, general health, baseline (preoperative) activity level and baseline (preoperative) condition of the knee and other joints.

4.3. POTENTIAL RISKS ASSOCIATED WITH OXFORD® CEMENTLESS PARTIAL KNEE SYSTEM REPLACEMENT

The safety and efficacy of the Oxford® Cementless Knee System has not been demonstrated clinically, and patients participating in the study may be subject to increased risks and/or adverse events, in addition to those listed under general surgical risks, including, but not limited to:

1. Excessive wear and loosening of implants due to migration of hydroxyapatite particles into the joint space
2. Failure of biologic fixation resulting in loosening of the implant

4.4. MINIMIZATION OF RISK

With the increased understanding of failure modes for mobile bearing knees, pre-clinical testing and clinical results found in the literature, it is believed that none of the previously mentioned adverse events will occur in significant numbers. This investigational plan has reduced the potential risk to the patient through the following methods:

1. By defining a patient population that limits the exposure of the device to patients conforming to the proposed indications, exclusions, and age requirements
2. By utilizing surgeon investigators who are licensed orthopedic surgeons that are trained in the usage of the Oxford® Cemented Partial Knee, thereby reducing surgical-related risk
3. Developing a surgical technique that may help eliminate potential operative difficulties

Prior to deciding whether to participate in the investigation, each subject will be provided with a description of all known potential complications and increased risks. Patients will also be provided with a description of alternate treatments. With this information and the counsel of their physician, patients will decide whether participation in the investigation and potential use of

the investigational device is in their best interest. The provision of this information and the patients' consent to participate in the investigation will be documented through the use of an Informed Subject Consent form.

Only licensed orthopedic surgeons who are practiced in partial knee replacement surgical procedures will be allowed to participate as clinical investigators for this investigation. General surgical risks will be controlled by surgeon adherence to accepted surgical guidelines and procedures. Risks related to the prosthetic design will be controlled by device labeling, and the investigators' adherence to the instructions for its safe handling and use.

The sponsor will further minimize the identified and/or emergent risks throughout the investigation by requiring the clinical investigators to document and report all complications and adverse effects to the investigation sponsor. Any unanticipated adverse device events will be reported to each clinical investigator, reviewing Institutional Review Board (IRB) and to the FDA. Based upon an evaluation of such events, the sponsor may either amend the investigational plan or terminate the investigation to protect the rights, safety and welfare of the subjects. Should an IRB decide to suspend or withdraw its approval for a clinical investigator to conduct the investigation at that institution based on unacceptable risks to the investigational subjects, the investigation sponsor will notify all reviewing IRBs, clinical investigators and the FDA of this action. To further minimize risks, any new information obtained during the course of the investigation relating to risks to the patient will be provided to subjects, investigators, and IRBs.

The investigation has been designed to minimize the number of patients exposed to the investigational device, yet provide sufficient numbers of subjects for valid scientific analysis of the compiled investigation data. The risks will be further controlled by the investigational design, the procedures for monitoring the dispensing of the investigational devices to the investigation subjects and the documentation, reporting and evaluation of the results from its surgical use.

The potential risks to the subjects in this investigation have been further minimized by the extensive preclinical and laboratory testing performed by the sponsor to verify the design requirements and the suitability for the intended use. Use of the investigational device is further supported by the reports from the medical and scientific literature for similar devices and the manufacturing processes and controls used to manufacture the prosthesis.

5.0 DESCRIPTION OF DEVICE

5.1. INVESTIGATIONAL DEVICE

The Oxford® Cementless Partial Knee System is a medial, unicompartmental prosthesis intended for use in primary knee replacement surgery. The system is designed to reduce pain and improve joint function in patients with osteoarthritis or avascular necrosis limited to the medial compartment of the knee.

The Oxford® Cementless Partial Knee System, which is the subject of this clinical investigation, comprises the following components:

- Porous + HA-coated universal femoral components for cementless fixation;
- Porous + HA-coated anatomic tibial components cementless fixation;
- Unconstrained meniscal bearing

5.1.1. FEMORAL COMPONENT[g]

The femoral component is universal in design in that they may be used on the left or right femur. The component is manufactured from cast CoCrMo alloy (conforming to ISO 5832). The outer, articulating surface of the femoral component is spherical and highly polished. The inner surface is spherically concave and concentric with the articulating surface, with two pegs (one central and one anterior) for component location and initial fixation. Posteriorly there is a small, flattened surface, the plane of which lies parallel to the axis of the central peg. The inner surface features a porous coating of plasma-sprayed titanium alloy, with plasma sprayed hydroxyapatite (ASTM F-1580) over this. The two pegs and an outer rail of the inner surface are only coated with the plasma sprayed hydroxyapatite and are not porous plasma sprayed. Five sizes of femoral component are available-extra small, small, medium, large, and extra-large.

5.1.2. TIBIAL COMPONENT

The tibial component is manufactured from heat-treated, cast CoCrMo alloy (conforming to ISO 5832-4) and is anatomic in design; each component is approximately semi-circular in shape, extending anteriorly for optimum bone coverage. The upper articular surface is highly polished and features a raised lip along the length of the lateral edge (located on the most lateral side of the medial compartment), called a vertical wall. The bone-contacting surface features a distally-protruding keel for component location and initial fixation. The keel, the recessed inferior surface of the tibial tray and lateral surface of the vertical wall feature a porous coating of plasma-sprayed titanium alloy, with an overlay of plasma-sprayed hydroxyapatite (ASTM F-1580). The anterior and posterior edges of the implant both feature recesses to allow for optimal impaction of the implant. Left- and right-side tibial components are each available in 7 sizes (AA, A, B, C, D, E, F), either with or without extractor slots.

[g] Images presented here are for graphical illustration only.

5.1.3. BEARING COMPONENT

The meniscal bearing is the same free-sliding, unconstrained bearing component that is used in the cemented Oxford® Unicompartmental Knee (Phase 3). It is composed of ArCom UHMWPE, in which is embedded a Ti6Al4V wire and 2 tantalum balls to act as radiological markers. The upper surface is spherically concave and designed for full congruency and area contact with the femoral component; the distal surface is flat, to allow it to articulate against the polished surface of the tibial component. The bearing edges are chamfered to minimize the risk of anterior impingement. The meniscal bearings are available in five sizes of left and right anatomic bearings (extra small, small, medium, large, and extra-large) are each available in 7 different thicknesses (3 to 9 mm, in 1 mm increments).

All of the implant components of the Oxford® Cementless Partial Knee System are manufactured using standard techniques well known in the production of orthopedic implant devices-i.e. CNC machining, turning, milling, drilling, blasting, linishing, polishing, Ti6Al4V- and HA-plasma spray coating, acid passivation (of metal components), laser etch marking, ultrasonic cleaning, clean packing and heat-sealing in packaging (under argon for UHMWPE) and terminal radiation sterilization. All implant components are supplied packaged sterile (terminally sterilized using a minimum of 25 kGy gamma radiation from a cobalt-60 source), for single use only.

The Oxford® Cementless Partial Knee System is intended to be used by suitably qualified orthopedic surgeons. Only surgeons who have completed FDA required Oxford® training course (P010014)will be allowed to participate in the study.

5.2. CONTROL DEVICE

The Oxford® Partial Knee System, which will be the control device for this clinical investigation, comprises the following components:

- Non-coated universal femoral components for cemented fixation;
- Non-coated anatomic tibial components cemented fixation;
- Unconstrained meniscal bearings

5.2.1. FEMORAL COMPONENT

The femoral components are manufactured from cast CoCrMo alloy. The outer, articulating surface of the femoral component is spherical and highly polished. The inner surface is spherically concave and concentric with the articulating surface, with two (one central and one anterior) fixation pegs for component location and initial fixation of the implant to bone. The entire bone-contacting inner surface has an Interlok®, rough blasted finish for cement adherence. Five sizes

of femoral component are available-extra small, small, medium, large, and extra-large. The control femoral component was approved in PMA supplement P010014/S026 on March 29, 2010.

5.2.2. TIBIAL COMPONENT

The tibial component is manufactured from cast CoCrMo alloy conforming to ISO 5832-4 and are anatomic in design; each component is approximately semi-circular in shape, extending anteriorly for optimum bone coverage. The upper articular surface is flat and highly polished with a raised lip 5.5mm high and 1.5mm thick running the length of the lateral edge, called a vertical wall. The cement/bone-contacting surface features a distally-protruding keel for component location and initial fixation of the implant to bone. The undersurface features a pocket to accept bone cement to aid in fixation. Left- and right-side tibial components are available in 7 sizes (AA, A, B, C, D, E, F).

5.2.3. BEARING COMPONENT

The meniscal bearing is composed of ArCom UHMWPE, in which is embedded a Ti6Al4V wire and 2 tantalum balls to act as radiological markers. The upper surface is spherically concave and designed for full congruency and area contact with the femoral component; the distal surface is flat, to allow it to articulate against the polished surface of the tibial component. The bearing edges are chamfered to minimize the risk of anterior impingement. The meniscal bearings are available in five sizes of left and right anatomic bearings (extra small, small, medium, large, and extra-large) are each available in 7 different thicknesses (3 to 9 mm, in 1 mm increments).

6.0 MONITORING PROCEDURES

The monitor for this study will be the Clinical Operations Department of the Sponsor located at:

Zimmer Biomet, Inc
1777 West Center Street
Warsaw, IN 46580

Monitoring will be conducted according to the most current version of the sponsor procedure. Please see Appendix J for a sample of this procedure.

7.0 LABELING

7.1. PACKAGE LABEL

Samples of the outer package label for the investigational Oxford® Cementless Partial Knee components are contained in **Appendix E**.

7.2. INSTRUCTIONS FOR USE (IFU)

A sample of the package insert (IFU) for the Oxford® Cementless Partial Knee femoral and tibial components is contained in **Appendix F**.

The meniscal bearings to be used with investigational cementless devices are identical to those used for the approved cemented Oxford® Partial Knee System. These components will receive the package insert approved for use with the cemented device (P010014). A copy of this insert is also contained in **Appendix F**.

7.3. SURGICAL TECHNIQUE

The surgical technique for the Oxford® Cementless Partial Knee is similar to that for the cemented device. Therefore, the same surgical technique will be employed for both the investigational and control devices with an addendum to the surgical technique being provided for the cementless device. A copy of cemented technique along with the addendum is contained in **Appendix G**. A list of the instrumentation to be used for implantation of the investigational device is contained in **Appendix H**.

8.0 CONSENT MATERIALS

A copy of the proposed informed consent for the study is contained in **Appendix I**.

9.0 OTHER INSTITUTIONS

Up to three independent radiographic reviewers may be involved with this study. The first radiographic reviewer will act as the primary reviewer. This person will review all required study films/x-ray views for the duration of the study.

If the primary reviewer identifies a radiographic failure, the films deemed a failure, along with a randomly selected statistical sample of current non-failures will be sent to a qualified, independent second reviewer. The second reviewer will not be informed of the number of failures and non-failures in the batch, nor will they be informed of which films have been deemed radiographic failures/non-failures in order to prevent any bias.

If the results of the second review differ significantly from the first, an independent, qualified third reviewer will then be employed to review the films. All reviewers will be required to examine the films as per the attached protocol in **Appendix D**, to ensure a standardized approach.

10.0 ADDITIONAL RECORDS AND REPORTS

Samples of the Case Report Form are contained in **Appendix C**.

11.0 CONCLUSION

This clinical investigation will be conducted under a well-defined protocol and subjects will be informed of the potential risks, benefits, and alternate treatments available prior to giving their consent for participation as investigational subjects. Exposure to the investigational device will be determined at random. Subjects' clinical course will be closely monitored and reported on throughout the investigation and new information provided to them that could affect their willingness to participate. The investigation has been designed to expose the lowest possible number of subjects to the investigational device that will still allow for a valid, scientific analysis of the reported data. The reporting and assessment of all untoward events arising during the course of the investigation will also be required. Therefore, the sponsor believes that all risks that are reasonably foreseeable have been identified and the means for adequately controlling those risks described.

APPENDIX A – OXFORD EXPLANT RETRIEVAL PROTOCOL

APPENDIX B-ANALYSIS OF SCIENTIFIC SOUNDNESS

Trial Objectives	The trial objectives are clear and concise and provide a basis for labeling indications for subsequent PMA submission.
Selection of Variables	• Outcome variables are controlled with carefully defined primary study endpoints. The endpoints are directly observable, objectively determined, and designed to reduce bias and error. • Influencing variables are controlled by the use of identical inclusion/exclusion criteria for the control and study populations. An extensive search of available literature and consultation with experts in the field were undertaken to discuss potential influencing variables (age, weight, gender, etc.) and these variables are not anticipated to effect study outcome.
Study Population	Inclusion/exclusion criteria have been developed by clinical experts and designers of the device. They are unambiguous and appropriately assess prognostic factors that may affect outcome variables.
Control Population	Concurrent controls are being used for this study. Control subjects will be assigned an alternative intervention and will remain under the direct care of the clinical study investigator.
Methods of Assigning Interventions	Blocked randomization will be used to assign intervention. A validated electronic system will be used to perform randomization.
Scientific Trial Design	The protocol addresses the treatment of study data that results from major and minor protocol deviations.
Sample Size Justification and Statistical Power	nQuery Advisor v. 7.0 was used to calculate the sample size for this study. Sample size calculation details are specified clearly in the analysis plan, and used 90% power, 5% Type I Error, and an 8% non-inferiority margin.
Blinding	Single blinding is being used in this study to avoid biased outcomes. Double and third party blinding cannot be undertaken due to the nature of the device. Secondary endpoints have been designed to further decrease potential bias.
Study Site and Investigator	Study sites and investigators have been carefully chosen for the study based on sufficient numbers of eligible patients, adequate facilities to support the protocol, prior clinical trial experience, and device specific experience.
Trial Monitoring	Trial monitoring plans are outlined in the protocol and supporting documents.
Baseline Evaluation	Baseline evaluations will be performed prior to subject entry

	into the trial. Six week follow up radiographs will serve as baseline for radiographic endpoints.
Intervention	Randomization will be performed with the use of a validated electronic system under the control of the Sponsor to ensure strict adherence to the protocol.
Follow Up	Mechanisms are in place to ensure that a high degree of subject compliance is maintained. Exclusion criteria have been designed to increase the likelihood of follow up by limiting disease states and other conditions that may interfere with the proposed follow up time period. The minimum duration of follow-up is two years. This is sufficient to capture anticipated effectiveness and to accurately estimate the rate of known or suspected adverse events. The duration of follow-up is identical for study and control populations.
Collection and Validation of Data	Validated methods for capturing data are currently in place and will be monitored for compliance throughout the trial.
Validation of Assumptions	Assumptions made for statistical methods will be checked before beginning a detailed analysis using these methods. If assumptions are not met, more appropriate tests will be used (e.g. non-parametric methods).
Hypothesis and Statistical Tests	The protocol clearly states the hypotheses to be tested and statistical tests to be used.
Pooling	Pooling is justified based on inclusion/exclusion criteria and adherence to the protocol will be strictly monitored and enforced to further justify pooling of study data.
Intent-to-Treat Analysis	An analysis of patients by the assigned treatment will be conducted in the sensitivity analyses for this study.

APPENDIX C-SAMPLE CASE REPORT FORMS

APPENDIX D-RADIOGRAPHIC PROTOCOL

APPENDIX E – PACKAGE LABELS

APPENDIX F-INSTRUCTIONS FOR USE

APPENDIX G-SURGICAL TECHNIQUES

APPENDIX H-LIST OF INSTRUMENTATION

APPENDIX I-SAMPLE INFORMED CONSENT

APPENDIX J- CLINICAL MONITORING PLAN