Randomized Controlled Clinical Outcomes of the Vanguard XP Bicruciate Knee System

ORTHO.CR.GK9B

Version 1

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STUDY SPONSOR

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Randomized Controlled Clinical Outcomes of the Vanguard XP Bicruciate Knee System

PROTOCOL NUMBER: ORTHO.CR.GK9B

PROTOCOL VERSION: V 1

STUDY SUMMARY

TITLE	Randomized Controlled Clinical Outcomes of the Vanguard XP Bicruciate Knee System
DESIGN	Prospective Controlled Multi-Center
PURPOSE	Compare the clinical outcomes of the Vanguard XP Bicruciate Total Knee System to the Vanguard CR Total Knee System
OUTCOME MEASURES	Patient Perception of recovery, Operative Room Procedure Time, Intraoperative complications; Anterior Cruciate Ligament (ACL) status; knee stability; readmissions, adverse events, pain, patient satisfaction, quality of life
POPULATION	306 knees, 5 surgeons
ELIGIBILITY	Patients will be included according to FDA cleared labeling of device in accordance with indications and contraindications for use.
DURATION	The study is anticipated to last no longer than 12 years which will include time for enrollment, data collection through ten years of follow-up and data analysis.

1. INTRODUCTION

1.1. BACKGROUND

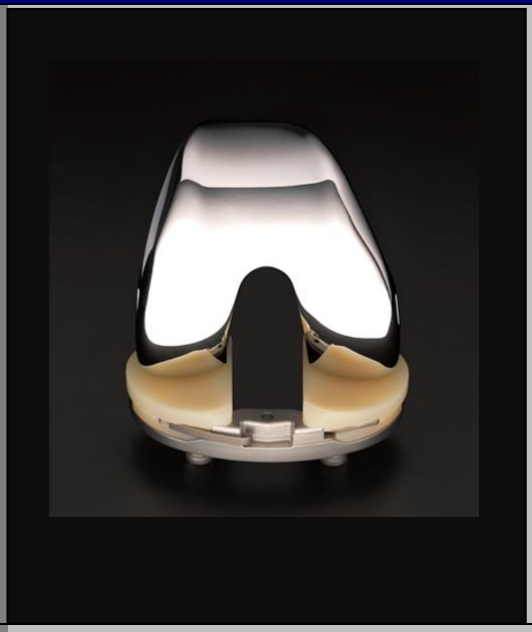
Early experiences with the Vanguard XP knee have been promising, with positive feedback on the early evaluation surveys. A randomized controlled trial is required to compare the clinical and patient reported outcomes with the Vanguard CR knee, which is well established. This study is designed to compare the clinical outcomes in patients who receive the Vanguard XP Knee System and patients who receive the Vanguard CR Femur with CR Bearing.

1.2. DEVICE DESIGN AND DESCRIPTION

Both knee systems included in this trial have been 510(k) cleared by the United States Food and Drug Administration (FDA). Both systems have the same indications for use (see section 3.1). The main difference between these total knee systems is that the Vanguard XP system requires a functional Anterior Cruciate Ligament (ACL), and the Vanguard CR system requires the anterior cruciate ligament to be sacrificed. Therefore the Vanguard XP Knee System is constrained by natural soft tissue, and the Vanguard CR is constrained by soft tissue and device design. Both systems allow the surgeon to retain the posterior cruciate ligament. Biomet knee joint replacement components include femoral, tibial, and patellar components. Components are available in a variety of designs and size ranges intended for both primary and revision applications. Specialty components are available including; femoral stems, femoral augments, tibial stems, tibial augments, tibial cement plugs and tibial screws.

For purposes of this study, in order to reduce variables with randomization, only patients receiving a primary total knee with a functional ACL will be enrolled. If the ACL is deemed not functional (either preoperatively or intraoperatively), the patients will be treated according to local standard of care and will not be enrolled into this study. A chart comparing the devices is provided:

Table 1.2-A

Device Comparison	*Vanguard XP Knee System*		*Vanguard CR Knee System*	
Picture				
Regulatory Status	FDA 510(k) Cleared		FDA 510(k) Cleared	
Basic Materials*	**Components**	**Materials**	**Components**	**Materials**
	Femoral Components	CoCrMo Alloy	Femoral Components	CoCrMo Alloy / Titanium Alloy
	Tibial Plates	CoCrMo Alloy	Tibial Plates	CoCrMo Alloy / Titanium Alloy
	Tibial Bearings	Ultra-High Molecular Weight Polyethylene (UHMWPE) α – tocopherol	Tibial Bearings	Ultra-High Molecular Weight Polyethylene (UHMWPE)
	Patellas	UHMWPE/Titanium Alloy/316LVM Stainless Steel	Patellas	UHMWPE/Titanium Alloy/316LVM Stainless Steel
	**Please consult the package insert for a complete list of FDA cleared component materials and risk analysis for each device.*			
Indications	Painful and disabled knee joint resulting from osteoarthritis, rheumatoid arthritis or traumatic arthritis where one or more compartments are involved; Correction of varus, valgus, or posttraumatic deformity; or Correction or revision of unsuccessful osteotomy, arthrodesis, or failure of a previous joint replacement procedure.		Painful and disabled knee joint resulting from osteoarthritis, rheumatoid arthritis or traumatic arthritis where one or more compartments are involved; Correction of varus, valgus, or posttraumatic deformity; or Correction or revision of unsuccessful osteotomy, arthrodesis, or failure of a previous joint replacement procedure.	
Contra indications	Infection, Sepsis, Osteomyelitis; Relative contraindications include: Uncooperative patient or patient with neurologic disorders who is incapable of following directions; Osteoporosis;		Infection, Sepsis, Osteomyelitis; Relative contraindications include: Uncooperative patient or patient with neurologic disorders who is incapable of following directions; Osteoporosis;	

Device Comparison	Vanguard XP Knee System	Vanguard CR Knee System
	Metabolic disorders which may impair bone formation; Osteomalacia; Distant foci of infections which may spread to the implant site; Rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram; Vascular insufficiency, muscular atrophy, neuromuscular disease; Incomplete or deficient soft tissue surrounding the knee.	Metabolic disorders which may impair bone formation; Osteomalacia; Distant foci of infections which may spread to the implant site; Rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram; Vascular insufficiency, muscular atrophy, neuromuscular disease; Incomplete or deficient soft tissue surrounding the knee.

1.3. RATIONALE FOR CURRENT STUDY

There is an increasing demand for joint replacement in a younger population(1). Due to the changing demographics of joint replacement, the younger population is seeking options that not only correct their disease or deformity, but do not limit them in activity. Activities of daily living are higher in this patient group, and patients needing total joint replacement do not have many options that accommodate this level of activity.

It is assumed that with preservation of ligaments, the knee will have more normal kinematics and therefore increased functional ability post-operatively, in comparison to traditional TKA that sacrifices soft tissue and stabilizes the knee with the device. There may be other advantages with preserving natural soft tissue that will be explored in a larger study, including restoration of natural kinematics, lower rate of loosening and polyethylene wear. This study will focus on knee stability, alignment of components, patient satisfaction, quality of life, intraoperative complications, re-admissions, and long-term survivorship.

1.4. PURPOSES

A. Compare patient perception of their knee implant feeling “normal / asymptomatic.”
B. Compare clinical outcomes through 2 year standard of care follow-up.
C. Evaluate patient perceived clinical outcomes and survivorship through 10-years of follow-up.

2. STUDY DESIGN

2.1. OVERALL DESIGN

Prospective Randomized Controlled clinical outcome study based in the United States.

2.2. STUDY GROUPS/TREATMENTS

A. Arm 1 (Control) : Vanguard CR Total Knee System

Patients who receive the cemented Vanguard CR femur with Vanguard CR Bearing based on meeting indications for use, and inclusion / exclusion criteria described in the protocol.

B. Arm 2: Vanguard XP Total Knee System

Patients who receive the cemented Vanguard XP BiCruciate Knee System based on meeting indications for use, and inclusion / exclusion criteria described in the protocol.

2.3. NUMBER OF SITES AND SUBJECTS/PROCEDURES

A total of 306 cases (knees) will be included in this study from four centers; 153 Vanguard CR and 153 Vanguard XP. Sample size calculation is provided in Section 8.1.

2.4. RANDOMIZATION

Patients will be randomized using a 1:1 blocked randomization scheme. Bilateral patients should be randomized by knee. Randomization will occur by enrolling the patient into Joint Assist and assigning an operative date. At that point the electronic database will assign the treatment group for the patient. The patient will be blinded from treatment until surgery has occurred.

2.5. PRIMARY AND SECONDARY ENDPOINTS

A. Primary Endpoint: Percentage of patients reporting their knee feels “normal”.

B. Secondary Endpoints: Patient Reported Outcome Measures “PROMs”, Knee Society Score, Complication Rate, Pain Relief, Functional outcomes, Survivorship

2.6. ASSESSMENT PROCEDURE

Table 2.6-A

Form	Pre-op (screening)	Operative (Enrollment)	Discharge	3 Mos	6 Mos	1 Yr	2 Yrs	3 Yrs	5 Yrs	7 Yrs	10 Yrs
Screening Log	X										
Informed Consent	X										
Demographics / Medical History	X										
Operative Form		X									
Modified Knee Society Score*	X		X	E†	SC***	X	X				
PROMS Questionnaire**	X		X	E†	SC***	X	X	X	X	X	X
Radiographs: AP, ML, Skyline			X	E†	SC***	X	X				
Radiographic Form			X			X	X				
Adverse Events		AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED
Withdrawals		AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED
Protocol Deviations		AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED	AS NEEDED

*Modified Knee Society Score includes an additional assessment of incidence of anterior knee pain. This additional question is exploratory and will not affect the total score of the KSS. In the event that a patient does not return for a visit, a partial "Phone Knee Society Score" can be completed and entered into the database.

**Patient Administered Outcome Scores "PROMS" Questionnaire can be collected in the office, over the phone, or via mailer. The questionnaire contains SANE/Patient Satisfaction, Oxford Knee Score, EQ-5D, KOOS, and the Forgotten Joint Score validated patient administered outcomes scores. These scores are combined into the paper version for easier administration to patients for completing. When entering to Joint Assist, these scores will be separated but contain the same exact questions.

***SC: 6 Month visit should be collected only if standard of care. Radiographs should be taken if standard of care at the center, however no radiographic form will be collected. Any adverse event or failure determined from radiographs should be documented on an adverse event form. All visits will be documented relative to the clinical site in the approved informed consent.

†"E" = exploratory and not required. If centers choose to collect 3-month data, they may although it is not required of this protocol. It should only be collected at centers where it is standard of care as an exploratory measure. Biomet will not reimburse for this milestone, but will allow data storage for centers that choose to document this to follow all standard of care visits. If this visit is followed, it must be included in the informed consent.

2.7. ASSESSMENT PARAMETERS AND METHODS

A. Source Documents & Data Collection Methods:

1. All data collected for this study will be collected through the sponsor's online database, Joint Assist. Centers may enter data directly to Joint Assist via any internet capable device with web browser capability. Devices that may be used include personal computers, laptops, iPads, etc. If using the paper case report forms for data entry, it will be required that the center then enter that data to Joint Assist.
2. Thorough training on Joint Assist will be completed with all investigators. Source documents that may be used include: direct entry to Joint Assist via computer or iPad, study supplied Case Report Forms which are later entered to Joint Assist, or may be medical records at the site which are also later entered into Joint Assist. A source document record should be recorded prior to study start.

B. Screening Log & Enrollment Form (Please also reference Section 3.3)

1. Pre-operative Screening**:**
    a. Patients will be screened according to the inclusion / exclusion criteria detailed in Section 3. Patient eligibility will be documented on the screening log. A pregnancy test should be performed if necessary, and negative results on file for all female subjects unless sterilized or post-menopausal to ensure subjects are not enrolled into the study who are pregnant.
2. Enrollment Form:
    a. Patient consent, study treatment assignment, and eligbility will also be documented on an enrollment form.

C. Center Level Information

1. Patient Expectations of Knee Replacement Recovery*
    a. Each center's standard of care method for managing patient expectations for total knee replacement recovery will be documented and sent to the sponsor.
2. Patient Rehabilitation*
    a. Each center's standard of care method for patient post-operative rehabilitation for total knee replacement recovery will be documented and sent to the sponsor.

**Not a research intervention, will be used for data analysis only. Not patient level data, and should be a summary of what is done as standard of care for all total knee patients at the center.*

D. Medical History and Demographic Data

1. Demographic information will be collected. Medical history will be obtained and a physical examination will be performed (including height and weight). Current medications, diagnosis, previous surgery, contralateral knee status, and comorbidities will also be recorded. Patient contact information (mailing address, phone number, and email address) will be collected in order to administer PROMS surveys either when a patient is unable to return for a clinical exam, or after the 2-year visit when the PROMS questionnaire is the only data point required.

E. Clinical Assessments

1. Intra-operative Data:
    a. An operative record will be completed to record details of each operative procedure and of the used implants. Operative room procedure time, tourniquet time, components used, and Intraoperative complications will be recorded on the operative record.

F. Clinical Outcomes

1. Data to determine the clinical and functional performance of the device will be collected. Pre-operative and post-operative analysis will be compared using recognized and validated systems:
    a. Modified Knee Society Score
        i. The American Knee Society Score is part clinical exam and part patient administered assessment of the knee. The objective part of the score, also known as the "knee score," should be collected in the clinic by qualified personnel. The functional and pain scores can be collected in

the clinic or via phone or mailer. An additional assessment of the incidence of "anterior knee pain" has been added to this CRF as an exploratory endpoint but does not affect the score. The full score will be collected preoperatively and at each post-operative visit through 2-years. After the 2-year visit, the patient administered portion will be collected with the PROMS Questionnaire by phone, email, or mailer from the patient.

b. Patient Reported Outcome Measures "PROMS"

i. A PROMS Questionnaire will be completed by the patient before surgery, and at each postop appointment indicated in the data collection table to assess the patient's perception of their knee replacement. This survey can be collected in the office, over the phone, or via mailer. The preoperative questionnaire contains the SANE, EQ-5D, Oxford Knee Score, and KOOS (The FJS and Patient Satisfaction questionnaires are only completed post-operatively). The postoperative questionnaire contains the SANE, Patient Satisfaction, FJS,EQ-5D, Oxford Knee Score, and KOOS validated patient administered outcomes scores.

G. Safety

1. *Adverse Events*: Please reference section **6,** and section **15** for Adverse event data collection method and definitions. Only serious and device related adverse events will be collected for this study. Patient hospital readmissions should be documented on an adverse event form, and the relation to the device documented.
2. *Revisions / Removals*: Please reference section **4** and section **15** for Revision / Removal data collection method and definitions.
3. *Withdrawals:* Please reference section **3.4** for detailed data collection methods, and section **15** for relative definitions.
4. *Protocol Deviations:* Please reference section **5** for Protocol Deviation data collection methods for this study.

H. Radiographic Assessments (including Radiographic Assessment protocol)

1. Views
   a. Standard Anterior-Posterior (AP)
   b. Standard Lateral View

c. Skyline merchant's view
d. Standing alignment (Long leg)

2. Placement
    a. The X-ray should show the total prosthesis including the entire length of the femoral and tibial stem.
3. Radiographic Collection Periods
    a. 0 to 12 weeks postoperative as baseline
        i. Standing Long Leg AP
        ii. Standard Short Films (AP, ML, Skyline)
    b. 1 Year Follow-up
        i. Standard Short Films (AP, ML, Skyline)
    c. 2 Year Follow-up
        i. Standard Short Films (AP, ML, Skyline)
4. Radiographic Assessment Form

    A radiographic assessment form will document the radiographic findings for each patient in this study. The 0-12 week films are to be used as baseline radiographic data for subsequent follow-up assessments / comparisons at 1 and 2 years post-op.

    a. Standing AP Long Leg Film: A standing long leg x-ray will be taken at 0-12 weeks in addition to standard films in order to document mechanical leg alignment.
    b. Standard Short Films:
        i. Assessments will be done according to the Knee Society Total Knee Arthroplasty Roentgenographic Evaluation[6] for:
            1. Alignment of components - (Standard Films)
            2. Radiolucent lines (RLL) - (Standard Films)
        ii. Migration/Subsidence – (Standard Films)

    c. If any osteolysis (a radiolucent line greater than 2mm in two or more zones that was not present on the 0-12 week x-ray) or gross shifting or migration of components (movement greater than 3mm or greater than 3 degrees as compared to the 0-12 week x-ray) is noted, it should be documented on a adverse event form.

2.8. ALLOWED WINDOW OF EACH SCHEDULE

A. Allowed Window of Each Schedule:

1. Discharge: 0-12 weeks
2. 6 months (+/- 2 weeks)
3. 1 year (+/- 2 months)
4. 2 years (+/- 2 months)
5. 3 years (+/- 2 months)
6. 5 years (+/- 2 months)
7. 7 years (+/- 2 months)
8. 10 years (+/- 2 months)

B. Each follow-up visit time point will be determined based on the date of surgery. All efforts should be made to bring patients back within the follow-up windows. Because this is a post-market study long-term study, patient visits that fall outside of window are allowable and will not be considered protocol deviations. The impact of the visit date will be assessed during data analysis.

2.9. DURATION OF THE STUDY

Based on time needed for multiple centers, the time required for IRB approval, the randomization of patients for enrollment and completed follow-up, the duration of this study is expected to be 12 years.

3. SELECTION AND WITHDRAWAL OF SUBJECTS

A. Process: Patients will be screened according to the inclusion / exclusion criteria detailed in Section 3.1 and 3.2. If a patient consents to participate but is found to be ineligible prior to commencement of first bony cut intraoperatively, this will be documented on the screening log.

B. Screen Failures: A screen failure can occur up to and prior to the first bony cut of the surgical technique. The ACL should be assessed intraoperatively to screen out any patients without sufficient soft tissue to participate, and if insufficient documented on the screening log as a screen failure. In the event that the patient receives a non randomized study device AFTER the first bony cut has commenced due to surgeon discretion, this patient is considered a randomization failure, but will still be followed in the study. Any patient consented that is a screen failure will not count towards the sample size, and will be replaced.

3.1. INCLUSION CRITERIA

Subjects will be considered for inclusion in this trial if they satisfy the following study criteria* and FDA cleared indications for use:

A. Cemented application of components*
B. Bilateral subjects randomized by knee*
C. Patients with pre-existing contralateral knee surgery*
D. Painful and disabled knee joint resulting from osteoarthritis, rheumatoid arthritis or traumatic arthritis where one or more compartments are involved.
E. Correction of varus, valgus, or posttraumatic deformity
F. Sufficient soft tissue surrounding the knee, including the Anterior Cruciate Ligament.

3.2. EXCLUSION CRITERIA

Subjects should be excluded from this trial if they satisfy any of the following study criteria* and contraindications for the device:

A. Cementless application of components*
B. BMI ≥40 kg/m^{2} *
C. Use of Anterior Stabilized Bearings*
D. Patients with severe pre-operative varus or valgus deformity ≥ 15 degrees*
E. Correction or revision of previous joint replacement procedure on index knee*
F. Infection
G. Sepsis
H. Osteomyelitis

Relative contraindications include:

I. Uncooperative patient or patient with neurologic disorders who is incapable of following directions
J. Osteoporosis
K. Metabolic disorders which may impair bone formation,
L. Osteomalacia
M. Distant foci of infections which may spread to the implant site
N. Rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram
O. Vascular insufficiency, muscular atrophy, neuromuscular disease
P. Incomplete or deficient soft tissue surrounding the knee, including the anterior cruciate ligament.*

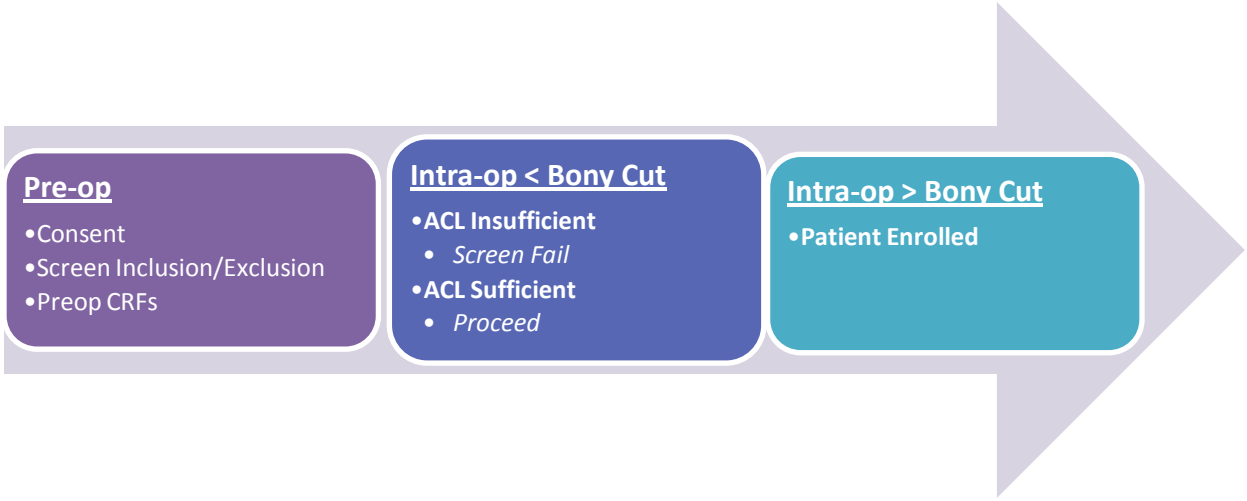
3.3. SUBJECT ENROLLMENT

A. Definition of Study Enrollment :

1. A patient is considered enrolled after they have been preoperatively screened for eligibility, consented to participate, and after surgeon's first intraoperative bony cut:
    a. Received a randomized study component.
    b. Received a non-randomized study component (randomization failure) due to surgeon discretion and standard of care at the local center.
2. Enrolled patients will be documented on the Enrollment form.

B. Randomization Failures:

1. A randomization failure is a patient who has been randomized but does not receive the intended randomized treatment. These patients' randomization assignments will not be re-used, and randomization should continue with the next patient being screened and consented.
    a. If the randomization failure occurs prior to the first bony cut, the patient is not considered "enrolled" and this should be documented on the screening log as a "screen failure" with the reason and rationale described (e.g. insufficient ACL). No further data should be collected on this patient. Screen failures do not count towards the sample size and will be replaced.
    b. If the randomization failure occurs after the surgery has commenced with the first bony cut, but due to the surgeon's discretion, the randomized treatment will not be the best treatment for the patient, the surgeon should implant according to their discretion and standard of care at the center. This patient counts toward the overall sample size and will not be replaced. Data should be collected on these patients per protocol.



3.4. SUBJECT WITHDRAWAL

A. ***Voluntary Participation***:

It is recognized that the subject's participation in this trial is entirely voluntary, and that she/he may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the investigator, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment. In event of subject withdrawal, applicable local procedures should be followed. Patients who are withdrawn from the study will not be replaced, and a Withdrawal form should be completed.

B. **Withdrawals:** All subject withdrawals must be documented on the Withdrawal Form. If withdrawal is due to patient death, or removal of components as indicated below, a withdrawal form should be completed. If the patient is withdrawn after receiving the randomized treatment, the subject will NOT be replaced.

C. If a patient receives a partial revision (patella or polyethylene replacement), or a reoperation (e.g.: manipulation), this should be documented on an adverse event form and the patient should continue to be followed in the study.

D. **Subject Withdrawal Criteria:**

1. If patients meet any of the following criteria, a subject withdrawal form should be completed, and below data documented on the form:
    a. Patient rescinds consent in writing: Date of occurrence
    b. Patient Death: Reason and date of death should be documented, and any relation to study device.
    c. Removal: Date of revision, all component part numbers removed, reason for revision, and any relation to study device.
    d. Revision of Metal* Components (Femur or Tibia): date of revision, all component part numbers removed, and reason for revision

**Bearing revisions in which only the polyethylene is replaced will not be withdrawn from the study.*

4. REVISION / REMOVAL

For subjects whom are revised in which a partial (revision) or full revision (removal) is conducted, an adverse event form should be completed. In patients in which metal or all components (removal) are removed, a withdrawal form should also be completed.

5. PROTOCOL DEVIATION MANAGEMENT AND REPORTING

Protocol deviations will be documented on a protocol deviation form. Sites and the sponsor may document protocol deviations. Any protocol deviation affecting patient treatment should be reported to the IRB as locally required. As this is not an investigational trial, protocol deviations affecting patient treatment are not anticipated, and out of window visits or missed visits will not be documented as protocol deviations.

6. ADVERSE EVENT MANAGEMENT AND REPORTING

A record of all device related and serious adverse events, including details of the nature, onset, duration, severity, relationship to the device, relationship to the operative procedure and outcome, will be made on the relevant section(s) of the Adverse Event Form. The subject should be questioned about progress with previously reported adverse event(s) at each subsequent follow-up assessment visit. Definitions to be used for adverse event reporting are included in section 15. Any serious or unanticipated adverse events should be reported to the sponsor as soon as possible, as it is required to report unanticipated adverse events to the FDA within 10 days of knowledge of the event.

7. IMPLANT RETRIEVAL AND ANALYSIS OF REMOVED IMPLANTS (if applicable)

Explanted devices should be returned to Biomet and may not be sent to any other laboratory facility. If your facility has the capacity to decontaminate the device prior to shipping, this is advised. If your device has not been decontaminated, you must ensure that all mailing instructions regarding biohazardous material are followed when returning the device to Biomet. The address for return of the item is:

Biomet Manufacturing
Attn: Clinical Research
Vanguard XP GK9B Study/Biohazardous Material (if not decontaminated)
56 East Bell Drive
Warsaw, IN 46582

8. STATISTICAL ANALYSIS

8.1. SAMPLE SIZE JUSTIFICATION

A. The primary goal of this study is to determine whether subjects receiving a Vanguard XP knee would feel more "normal/asymptomatic" than subjects who are implanted with a Vanguard CR knee. This will be achieved using Pearson Chi-Square test for two independent proportions.

Fixed Scenario Elements	
Distribution	Asymptotic normal
Method	Normal approximation
Number of Sides	2
Null Proportion Difference	0
Group 1 Proportion	0.66
Group 2 Proportion	0.83
Alpha	0.05

B. Based on these assumptions, 137 patients will give 90% power to detect a 17 percent difference between groups with regard to the percentage of patients who report their knee as feeling "normal". We increase our sample size by 10% to allow for patients who do not follow up for various reasons. This gives a sample size of 153 for each group and a total of 306 patients.

8.2 ANALYSIS OF THE PRIMARY STUDY ENDPOINT

The statistical test used in the primary analysis will be a two-sided Pearson's chi-square test for the difference in independent proportions. The null hypothesis will be rejected if $p < 0.05$ for this test.

8.3 ANALYSIS OF BASELINE, SAFETY, AND SECONDARY EFFICACY STUDY DATA

MODELS FOR CONTINUOUS MEASURES

Comparisons of Vanguard XP vs Vanguard CR with regard to continuous baseline, safety, and secondary outcomes will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of the measures being analyzed. A t-test, Wilcoxon test, or one-way ANOVA (as appropriate) will be performed to assess differences.

CATEGORICAL DATA ANALYSES

Comparisons of Vanguard XP vs Vanguard CR with regard to categorical baseline, safety, and secondary outcomes will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of the measures being analyzed. Specifically, categorical outcomes will be compared for investigational and control groups using the Fisher's Exact test (for 2x2 tables with small sample sizes that do not satisfy assumptions for likelihood ratio chi-square test) or the Likelihood Ratio chi-square test.

9. HANDLING OF MISSING AND INCOMPLETE DATA

It is required that data be entered into the secure online database, Joint Assist. A review of data will be made at the beginning of each month to monitor the completeness of each required milestone. Missing or incomplete data will not be reimbursed. It is imperative that all required data is collected at the appropriate time window and entered in to Joint Assist in a timely manner. Data reimbursement will not begin until a complete enrollment (preop, operative and 0-12 week visit) is entered into Joint Assist. If a patient misses a visit, and refuses to return for a clinical exam, a "Phone Follow-up KSS," and "PROMS Questionnaire" case report form can be completed at the discounted rate (if applicable) defined in the investigator agreement. If that event occurs, the Knee Society objective score would not be collected.

10. DATA COLLECTION, HANDLING AND RETENTION

10.1. SOURCE DOCUMENTATION REQUIREMENTS

A. Source documentation for this study will be maintained to document the treatment and study course of a subject and to substantiate the integrity of the trial. Source documentation will include, but not be limited to, paper or electronic case report forms, hospital and/or clinic or office records documenting subject visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, radiographic images, pharmacy records, and medical consultations (as applicable).

10.2. CASE REPORT FORMS

A. Data for this clinical trial will be collected and documented on the subject Case Report Forms (CRFs) provided which may be in paper form or in an electronic form. The paper case

report forms match the electronic case report forms. The paper case report forms can be used as an example of the electronic case report forms in the event the IRB requires review of CRFs.

Authorized study site personnel will complete CRFs only. CRFs must be reviewed and signed by the Investigator or his/her designees as applicable or required by the CRF. Electronic CRFs, via the online database Joint Assist, will utilize user-authentication via user name and password, to apply electronic signature to CRFs. Any data entered to the database is managed with an audit trail that will record the user name of all those entering and / or changing data in this study.

10.3. ELECTRONIC DATA ENTRY (where appropriate)

A. When using electronic trial data handling and/or remote electronic trial data systems, the sponsor will:

1. Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).
2. Maintains SOPs for using these systems.
3. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
4. Maintain a security system that prevents unauthorized access to the data.
5. Maintain a list of the individuals who are authorized to make data changes.
6. Maintain adequate backup of the data.

11. DATA REPORTING

11.1. ANNUAL REPORT

A. Once all centers are enrolled, and data is available, an annual report will be written by the sponsor for purposes of IRB renewal. Data included in this report will be general demographics, adverse events, revisions / reoperations, subject withdrawals, and protocol deviations. The report will summarize data for the entire study. Site level reports and specific data queries are available upon request.

11.2. FINAL REPORT

A. Once the study is complete, a final report will be documented with primary and secondary endpoint analysis. This report will be distributed to all participating centers within 6 months of completion of the study.

12. RISK ANALYSIS

Please reference the risk analysis provided in the package insert for each device that is available as a part of the investigator binder.

13. MONITORING PLAN

Monitoring is not required for post-market studies, however, Biomet, as the sponsor of this study, may monitor the data collection to ensure that the investigation is being conducted consistent with the protocol. A pre-investigational visit or training webinar is required for all sites, and routine monitoring (onsite or in-house) of the quality of the data will be completed at minimum, annually.

13.1. PRE INVESTIGATIONAL SITE VISIT:

A. Prior to initiation of the study, the study manager will provide the Investigator with all the necessary information to enable him to carry out his responsibilities. This prepares the site with an in-depth training on the protocol, case report forms, and data collection process for the length of the study. The study manager or designee will also train the site on using the Biomet Joint Assist database. This visit may be done by physical visit to the site, or training via webinar.

13.2. STUDY CLOSE-OUT

A. At the end of the study, an effort to resolve all pending data queries will be completed to ensure the integrity of the data for final data analysis.

14. ETHICAL AND REGULATORY REQUIREMENTS

14.1. CODE OF CONDUCT

A. The Investigator will ensure that the clinical study is conducted in accordance with
   1. Protocol
   2. Regulatory and IRB/EC requirements

14.2. REGULATORY APPROVAL

A. The devices being studied are post-market non-investigational devices cleared by the FDA via 510(k) regulatory pathway. The Vanguard CR Knee System was originally cleared as a part of 510(k) K023546 and was called the "Maxim Accel" Knee, later branded as "The Vanguard Total Knee System" in January of 2003. The Vanguard XP Knee system was cleared via 510(k) K122160 in March of 2013. The patients included in this study would receive knee replacement without participating in the study. This study is as a post market surveillance study for purposes of better understanding implant performance and patient perceived assessment of their recovery.

14.3. INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEE

A. The Investigator must obtain appropriate Institutional Review Board (IRB) approval before the study can be initiated. The investigator should assess if there are any local IRB requirements, and either gain approval through local IRB, or through a commercial IRB. A copy of the written approval from the IRB and a copy of the approved informed consent form should be sent to the Sponsor.

B. Any changes to the protocol must be discussed and approved by the Sponsor in writing unless the change is made to assure the safety of the subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by the Sponsor for submission to the IRB for review and approval prior to initiation of the change. Any change made emergently must be documented in the subject's medical record and reported to the Sponsor within the time period required by local SOPs and applicable regulations.

C. The Investigator must immediately forward to the IRB any written safety reports or updates from the Sponsor. The Investigator must keep the IRB informed of the progress of the study as required by the IEC but at least annually.

14.4. INFORMED CONSENT

A. All patients require informed consent due to the research interventions and data collection required of this study. Subjects (or the subject's legally authorized representative) will be provided with an informed consent in order to give ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study procedures begin. If the subject agrees to participate in the study, the

subject/representative must sign the informed consent form. The Investigator or his/her qualified designee must also sign the informed consent form. A copy of the informed consent form should be given to the subject/representative. All subjects who meet all of the entry criteria will be considered for inclusion in this trial. Any subject meeting any of the exclusion criteria will be excluded from the trial.

B. The informed consent form must be approved by the institution's IEC/IRB.

C. Subjects will be informed of new information learned during the study, which may affect the subject's decision to continue participation in the study.

D. An enrollment case report form will document for the sponsor that the center has obtained the required signed informed consent form. Fully signed informed consent forms (or copies) are to be maintained in the study file by all centers, and must be available for verification by monitors or inspectors.

14.5. SUBJECT CONFIDENTIALITY

A. General Responsibilities:

1. The Sponsor and centers will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records. The Sponsor will also instruct the study investigators in the importance of maintaining the confidentiality of study records. The records will be made available as required for review by governing regulatory agency such as FDA and a reviewing IEC/IRB, however to the extent possible, the subject's identity will not be disclosed.

B. Electronic Data Capture

1. Once the site enters a patient into Joint Assist, the database will assign that patient an ID number. It is the responsibility of the investigator to maintain a list of patient identification and Joint Assist ID numbers throughout the course of the study. By assigning patients a unique ID number, their identity is protected in Joint Assist, the online database. The database is restricted, allowing a doctor to only view and enter data from his own patients. User authentication is required to view research data. The data is transmitted to a centralized database through a secured (SSL) channel on the Internet. Data in transit is in 128-bit encryption. The access to the centralized database is limited to those who are responsible for maintaining the database.

15. STUDY DEFINITIONS

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

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

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

D. **Adverse Events:** Adverse events will be documented according to ISO 14155:2011definitions as follows. Since this is not an investigational medical device study (post market study), "investigational" has been removed from the definition. For the purposes of this study, only adverse events meeting the following criteria will be included, unless otherwise reported at the discretion of the investigator:

E. **Serious Adverse Event (SAE):** adverse event that:

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

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

F. **Adverse Device Effect (ADE):** adverse event related to the use of a medical device; this includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device; includes any event resulting from user error or from intentional misuse of the medical device.

G. **Serious Adverse Device Effect (SADE):** adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

H. **Unanticipated Serious Adverse Device Effect (USADE):** serious adverse device affect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

I. Withdrawal

Occurrence of death, rescinded consent, randomization failure after surgery commenced, or when the subject has a complete removal, or revision of metal components (femoral component / tibial tray).

16. REFERENCES

1. *Kurtz, SM, et al. Future Young Patient Demand for Primary and Revision Joint Replacement. CORR. 467:10; 2009: 2606-2612.*

2. *Robertsson, O, et al. Patient Satisfaction after knee arthroplasty. Acta Orthop Scand. 2000; 71 (3): 262-267.*

3. *Behrend, H, et al. The "Forgotten Joint" as the Ultimate Goal in Joint Arthroplasty. The Journal of Arthroplasty. 2012. 27(3):430-436e1.*

4. *Insall, JN, Dorr, LD, Scott, RD and Scott, WD Rationale of the Knee Society Clinical Rating System. Clinical Orthopedics & Related Research. 1989. 248, 13-14.*

5. *Brooks, et al. (Eds.). (2003) The Measurement and Valuation of Health Status Using EQ-5D: A European Perspective. Netherlands: Kluwer Academic Publishers.*

6. *Ewald, FC. The Knee Society Total Knee Arthroplasty Roentgenographic Evaluation and Scoring System. Clinical Orthopedics & Related Research. 1989. 248, 9-12.*

SIGNATURE PAGE

Protocol authorized by (Project Leader):

Name & Role	Date	Signature
Megan King Manager, Clinical Operations	January 15, 2014	