NexGen® TM Tibia Clinical Outcomes Study

PROSPECTIVE MULTICENTER STUDY OF THE *NexGen® TM Monoblock and Modular Tibias*

Protocol #K.CR.I.G.16.34
U.S.

July 17, 2017 – Version 1.0

STUDY SPONSOR
Zimmer, Inc.
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Appendices:

I. Document History

Version	Date	Description of Change	Author/Revised By
1.0	17-JUL-2017	Initial Document	Scott Abshagen

II. Study Synopsis

STUDY TITLE	NexGen® TM Tibia Clinical Outcomes Study
SPONSOR	Zimmer Inc., Warsaw, Indiana
PROTOCOL #	K.CR.I.AM.16.34
STUDY DEVICES	• **Zimmer TMT: NexGen® Trabecular Metal Monoblock Tibias** (referenced as *NexGen* TM Monoblock Tibia throughout protocol) • **Zimmer, Inc: NexGen® Trabecular Metal Tibial Trays** (referenced as *NexGen* TM Modular Tibia throughout protocol) Cementless tibias used with the NexGen® Knee System or Persona® femoral.
STUDY OBJECTIVE	The objective of this study is to evaluate clinical performance for the commercially available *NexGen* TM Monoblock Tibia and *NexGen* TM Modular Tibia used in primary cementless tibia total knee arthroplasty. The assessments will include: 1. Clinical performance measured by radiographic parameters, pain and function, and survival of the device. 2. Safety based on incidence and frequency of adverse events.
ENDPOINTS	**Primary Endpoint:** The primary endpoint of this study is to evaluate the clinical performance of the implant at 2 years postoperatively using radiographic parameters. Radiographs will be assessed for the absence of progressive tibial radiolucencies, as defined in the radiographic protocol. **Secondary Endpoints:** The secondary endpoints of this study will evaluate the clinical performance of the implant at 2 years postoperatively, based upon: • No revisions for any reason • Oxford Knee Score (OKS) >38
TARGET POPULATION	Patients qualifying for primary cementless tibia total knee arthroplasty who meet the inclusion/exclusion criteria for study participation.
STUDY DESIGN	Prospective, multicenter, non-randomized, non-controlled
STUDY TYPE	Post Market Outcomes Study
SAMPLE SIZE	A minimum of 132 subjects are to be enrolled in this study. • Approximate equal distribution with at least 66 *NexGen* TM Monoblock and 66 *NexGen* TM Modular subjects. • Up to 10 U.S. sites, each contributing between 22 to 30 subjects. • Each site will be selected for a specific *NexGen* TM device, either the Monoblock or Modular design. • The *NexGen* TM Monoblock Tibia and *NexGen* TM Modular Tibia are considered 2 single-arms being analyzed separately.

LENGTH OF STUDY	4 years (6 months enrollment, 2 years follow-up, and interval windows) • Enrollment/Preoperative • Immediate Postop Radiograph (Pre weight-bearing) • 6 weeks (± 2 weeks) • 6 months (± 1 month) • 1 year (± 1 month) • 2 years (± 2 months)
SCORES	Forgotten Joint Score (FJS-12) Oxford Knee Score (OKS) UCLA Activity & Satisfaction Survey
RADIOGRAPHS	AP and Lateral X-rays will be required of the operative knee immediate postop and at each clinical follow-up visit. Radiographs will be reviewed for image quality by the surgeon during the subject's clinical visit. Radiographic images must show an orthogonal view of the tibial implant interface. Study radiographs will be requested from sites for independent radiographic review.
INCLUSION CRITERIA	INCLUSION CRITERIA: 1. Patient is at least 18 years of age. 2. Patient qualifies for a primary cementless tibia total knee arthroplasty based on physical exam and medical history, including diagnosis of severe knee pain and disability due to at least one of the following: a. Rheumatoid arthritis, osteoarthritis, traumatic arthritis, polyarthritis. b. Collagen disorders and/or avascular necrosis of the femoral condyle. c. Post-traumatic loss of joint configuration, particularly when there is patellofemoral erosion, dysfunction or prior patellectomy. d. Moderate valgus, varus, or flexion deformities. e. The salvage of previously failed surgical attempts that did <u>not</u> include partial or total knee arthroplasty of the ipsilateral knee. 3. Patient has participated in the study-related Informed Consent process. 4. Patient is willing and able to provide written Informed Consent by signing and dating the IRB approved Informed Consent Form. 5. Patient is willing and able to complete scheduled study procedures and follow-up evaluations as described in the Informed Consent Form. 6. Independent of study participation, patient is a candidate for commercially available cementless *NexGen* TM tibial knee component, implanted in accordance with product labeling.

EXCLUSION CRITERIA	EXCLUSION CRITERIA: 1. Previous history of infection in the affected joint. 2. Active local or systemic infection that may affect the prosthetic joint. 3. Insufficient bone stock on femoral or tibial surfaces. 4. Skeletal immaturity. 5. Neuropathic arthropathy. 6. Osteoporosis or any loss of musculature or neuromuscular disease that compromises the affected limb. 7. A stable, painless arthrodesis in a satisfactory functional position. 8. Severe instability secondary to the absence of collateral ligament integrity. 9. Rheumatoid arthritis accompanied by an ulcer of the skin or a history of recurrent breakdown of the skin. 10. Patient has previously received partial or total knee arthroplasty for the ipsilateral knee. 11. Patient is currently participating in any other surgical intervention studies or pain management studies. 12. Patient is known to be pregnant or considered a member of a protected population (e.g., prisoner, mentally incompetent, etc.). 13. Patient has a known or suspected sensitivity or allergy to one or more of the implant materials.
STATISTICAL REPORTING	Clinical performance will be evaluated for radiographic success, pain and function, and implant survival by summarizing the data descriptively. Categorical data (e.g., gender, component size) will be reported using frequency and percentages with 95% Confidence Interval (CI) over the time periods of interest. Continuous data (e.g. age, weight) will be summarized using mean, standard deviation, minimum, median, maximum, and 95% CI over the time periods of interest. Implant survival will be summarized using a Kaplan-Meier method and presented with rates (expressed as percentages) and CI. Routine summaries of complication data will be in the form of frequencies and percentages.

This protocol is written based on guidelines from ISO 14155:2011 Standard for Clinical Investigation of Medical Devices For Human Subjects – Good Clinical Practice [1] and is in accordance with US Code of Federal Regulations 21 CFR Parts 11, 50 and 56 [2].

III. Data Collection Overview

The following tables indicate required forms and activities to be completed at the given time point:

Form Name	Preop	Surgical to Immediate Postop	6 Weeks Postop (± 2 weeks)	6 Months Postop (± 1 month)	1 Year Postop (± 1 month)	2 Years Postop (± 2 months)
Site and Subject completed:						
Informed Consent Form	X●					
Site completed:						
Inclusion/Exclusion Criteria	X					
Demographic Evaluation	X					
Surgical & Discharge Information		X				
Physical Exam	X		X	X	X	X
Physician Assessment of Postop Radiographs		X	X	X	X	X
Subject completed:						
Forgotten Joint Score (FJS-12)	●		●	●	●	●
Oxford Knee Score (OKS)	●		●	●	●	●
UCLA Activity & Satisfaction Survey	●		●	●	●	●
Site completed as applicable:						
Adverse Event Report		★	★	★	★	★
Protocol Deviation	★	★	★	★	★	★
Study Completion	★	★	★	★	★	★
Explanted Device Form			★	★	★	★

Activity	Preop	Immediate Postop	6 Weeks Postop	6 Months Postop	1 Year Postop	2 Years Postop
Radiograph Submission		X	X	X	X	X

X Site completed (Investigator or designee)
● Subject completed
★ Site completed as applicable (Investigator or designee)

The following table indicates required forms to be completed by the site for revision patients:

Form Name	Comments
Physician Assessment of Postop Radiographs	Mark the "Pre-Revision" exam period.
Adverse Event Report	Document adverse event resulting in the revision.
Study Completion	Complete indicating "Study Prosthesis Removed" under Study Completion Status.
Explanted Device Form	Document explanted device information. Send explanted device to Zimmer Biomet per Appendix F.
Medical Device Reporting Information Form (MDRIF):	If device-related, complete MDRIF form (Appendix E) and forward the form and all applicable supporting documents to Zimmer Biomet within 7 days. The supporting documents include: ▪ Operative reports (index and revision surgery) ▪ Radiographs (immediate postop, intermediate, and pre-revision)

IV. Introduction and Purpose

In recent years the advent of highly porous trabecular metal implants in cementless fixation has brought the cemented vs. cementless debate back to the forefront among surgeons when determining best practices and benefits to patients. Fricka, et al [3], describe the potential benefits of cementless fixation as preservation of bone stock, shorter operating room time (and thus a cost savings), ease of revision if necessary, and elimination of any complications associated with cemented fixation such as third body wear and retained loose fragments. Potential disadvantages are the lack of surgeon experience implanting the modular tibial tray, cost of such implants, and determining if there is an ideal patient population for implantation of such devices.

To address clinical challenges and methodologically address implant characteristics, a prospective, multi-center, longitudinal data collection model is being proposed for *NexGen* TM Tibia components used in primary cementless tibia total knee arthroplasty.

V. Study Objectives

The primary objective of this study is to evaluate clinical performance for the commercially available *NexGen* TM Monoblock Tibia and *NexGen* TM Modular Tibia used in primary cementless tibia total knee arthroplasty. This will be done by analysis of radiographic parameters and validated patient report outcome measurements as well as monitoring adverse events and survivorship of the implant.

The assessments will include:

1. Clinical performance measured by radiographic parameters, pain and function, and survival of the device.
2. Safety based on incidence and frequency of adverse events.

VI. Study Design

This is a prospective, multicenter, non-randomized clinical study designed to facilitate the collection and evaluation of radiographic parameters, pain and function, survival of the device, and adverse event data. This clinical study will include the *NexGen* TM Monoblock Tibia and *NexGen* TM Modular Tibia as 2 single-arms being analyzed separately.

The primary endpoint of this study is to evaluate the clinical performance of the implant at 2 years postoperatively using radiographic parameters. Radiographs will be assessed for the absence of progressive tibial radiolucencies, as defined in the radiographic protocol.

The secondary endpoints of this study will evaluate the clinical performance of the implant at 2 years postoperatively, based upon:

- No revisions for any reason
- Oxford Knee Score >38

A minimum of 132 subjects are to be enrolled in this study, with approximate equal distribution of at least 66 *NexGen* TM Monoblock and 66 *NexGen* TM Modular subjects. A maximum of 10 U.S. sites will contribute, each enrolling between 22 to 30 implanted knees. Each site will be selected for a specific *NexGen* TM device, either the Monoblock or Modular design.

Investigators will be skilled in cementless total knee arthroplasty and experienced implanting either the *NexGen* TM Monoblock Tibia or the *NexGen* TM Modular Tibia.

Each Principal Investigator will be responsible for obtaining Institutional Review Board (IRB) approval as required prior to conducting the study. In order to avoid potential selection bias, each Investigator will offer study participation to each consecutive eligible patient presenting as a candidate for primary cementless tibia total knee arthroplasty using the *NexGen* TM Monoblock or *NexGen* TM Modular Tibia. Eligible candidates who express interest in study participation will be offered Informed Consent. All potential study subjects will be required to participate in the Informed Consent process and will not be considered enrolled in the study until the candidate has signed and dated the IRB approved Informed Consent Form. Study data cannot be collected until the candidate has completed the Informed Consent process and signed and dated the IRB approved Informed Consent Form.

All study subjects will undergo preoperative clinical evaluations prior to their cementless tibia total knee arthroplasty. An immediate postoperative radiograph will be required. Postoperative clinical follow-up and radiographic evaluations will be conducted at 6 weeks, 6 months, 1 year, and 2 years.

The Investigator will review radiographs immediately postop and at each clinical evaluation to ensure the radiographs meet the protocol requirements. The Sponsor will provide a radiographic protocol (Appendix D) to assist sites in proper x-ray technique in order to assure adequate images are captured for study analysis.

The Sponsor will request copies of these radiographs for independent radiologic review. The Sponsor will request one central reviewer for all radiographs independent of the surgeon and institution.

VII. Study Population

The study population for primary statistical analysis will be comprised of subjects who require primary cementless tibia total knee arthroplasty and satisfy the inclusion/exclusion criteria outlined in this section of the protocol. In order to avoid potential selection bias, Investigators will offer study participation to each consecutive eligible patient presenting as a candidate for primary cementless tibia total knee arthroplasty using the commercially available *NexGen* TM Monoblock or *NexGen* TM Modular Tibia implants. Eligible candidates who express interest in study participation will be offered Informed Consent. The **Inclusion/Exclusion Criteria** should not be completed until the study-specific Informed Consent Form has been completed.

A. Inclusion Criteria

1. Patient is at least 18 years of age.
2. Patient qualifies for a primary cementless tibia total knee arthroplasty based on physical exam and medical history, including diagnosis of severe knee pain and disability due to at least one of the following:
    a. Rheumatoid arthritis, osteoarthritis, traumatic arthritis, polyarthritis.
    b. Collagen disorders and/or avascular necrosis of the femoral condyle.
    c. Post-traumatic loss of joint configuration, particularly when there is patellofemoral erosion, dysfunction or prior patellectomy.

d. Moderate valgus, varus, or flexion deformities.
e. The salvage of previously failed surgical attempts that did not include partial or total knee arthroplasty of the ipsilateral knee.

3. Patient has participated in the study-related Informed Consent process.
4. Patient is willing and able to provide written Informed Consent by signing and dating the IRB approved Informed Consent Form.
5. Patient is willing and able to complete scheduled study procedures and follow-up evaluations as described in the Informed Consent Form.
6. Independent of study participation, patient is a candidate for commercially available cementless *NexGen* TM tibial knee component, implanted in accordance with product labeling.

B. Exclusion Criteria

1. Previous history of infection in the affected joint.
2. Active local or systemic infection that may affect the prosthetic joint.
3. Insufficient bone stock on femoral or tibial surfaces.
4. Skeletal immaturity.
5. Neuropathic arthropathy.
6. Osteoporosis or any loss of musculature or neuromuscular disease that compromises the affected limb.
7. A stable, painless arthrodesis in a satisfactory functional position.
8. Severe instability secondary to the absence of collateral ligament integrity.
9. Rheumatoid arthritis accompanied by an ulcer of the skin or a history of recurrent breakdown of the skin.
10. Patient has previously received partial or total knee arthroplasty for the ipsilateral knee.
11. Patient is currently participating in any other surgical intervention studies or pain management studies.
12. Patient is known to be pregnant or considered a member of a protected population (e.g., prisoner, mentally incompetent, etc.).
13. Patient has a known or suspected sensitivity or allergy to one or more of the implant materials.

VIII. Study Device Information

NexGen knee components included in this study are the *NexGen* TM Monoblock Tibia or *NexGen* TM Modular Tibia. Both the *NexGen* TM Tibias are designed specifically to adhere to bone through the use of trabecular metal technology. These devices are intended for long-term implantation in accordance with product labeling. Please refer to the package insert for additional information and instructions.

IX. Study Procedures

A. Offer Study Participation

Study participation will be offered to each consecutive eligible patient presenting as a potential candidate for primary cementless tibia total knee arthroplasty using the commercially available *NexGen* TM Monoblock or *NexGen* TM Modular Tibia implants, depending on the clinical site's

device designation. A **Subject Enrollment Log** (Appendix C) will be completed to document all individuals screened as potential candidates for the study. Eligible candidates who express interest in study participation will be offered Informed Consent. Prior to patient involvement in the study, the patient must participate in the Informed Consent process and sign and date the IRB approved Informed Consent Form.

B. Informed Consent Process

For candidates that express interest, the Investigator or Designee will describe relevant study information, including the purpose, procedures, possible risks, and potential benefits associated with study participation. The Investigator or Designee will also review, along with the candidates, the Informed Consent Form approved by both the governing IRB and the study Sponsor. Candidates shall have sufficient time to read and understand the IRB approved Informed Consent Form and discuss whether they wish to participate in the study. Candidates will be asked to acknowledge whether all of their questions and concerns have been addressed to their satisfaction. Any questions that candidates may have will be addressed appropriately by the Investigator or Designee. Candidates will be further instructed that they are free to obtain additional information from the Investigator or Designee at any time, that they are free to decline participation, and that they are free to withdraw their consent and discontinue their participation at any time without prejudice.

After completing the Informed Consent process, candidates who agree to enter the study must sign and date the IRB approved Informed Consent Form. The Informed Consent Form must be signed and dated prior to study data collection and the date of study surgery. For bilateral TKA candidates that agree to enroll for both operative sides, a separate Informed Consent Form must be signed and dated for each operative side.

A copy of the signed Informed Consent Form should be provided to the subject. The original signed Informed Consent Form is to be filed in the subject's study binder.

Study data will not be collected until the Informed Consent Form has been signed and dated. If the candidate does not wish to participate (does not sign and date the Informed Consent Form), data for that candidate will not be collected for this study.

C. Subject Enrollment

Once the Informed Consent Form has been signed and dated by the subject, the subject will be considered enrolled in the study. A unique case identification number (Case ID) will be assigned to each participating subject/knee (bilateral subjects will be assigned a unique case ID number for each knee). This unique case ID number will be used throughout the study for identification. Case ID numbers will be assigned consecutively in ascending order per site, with the starting number for a given site defined by the Sponsor.

The subject will be considered an active study subject after receiving the study device during surgery. In the event that a subject does not receive the study device at the time of surgery, a **Study Completion** form must be submitted and this will be documented as a screen failure.

D. Subject Enrollment Log

A **Subject Enrollment Log** (Appendix C) will be maintained at the site throughout the course of

the study and filed in the site Regulatory Binder. The purpose of the log is to provide documentation that all enrolled study subjects underwent the Informed Consent process. All candidates who sign and date the approved Informed Consent Form for the study must be entered in the log. If a subject signs and dates additional Informed Consent Form(s) after enrollment (e.g., due to a protocol amendment, protocol revisions, etc.), subsequent signings will also be recorded in the log. The proposed date of surgery for each subject will also be added to the log.

E. Monitor Log

The **Monitoring Visit Log** (Appendix C) will be maintained throughout the course of the study. The log will contain the visit date, monitor name/signature and the purpose of the visit (i.e. site initiation, onsite interim monitoring, site close-out, etc.). The monitoring visit log will be filed in the site Regulatory Binder for the study.

F. Delegation of Authority

A **Delegation of Authority Log** (Appendix C) will be maintained throughout the study and will contain the names, initials, signatures and study responsibilities of all site personnel/designees involved in study procedures and data collection. The **Delegation of Authority Log** will be filed in the site Regulatory Binder for the study.

G. Preoperative Data Collection

Preoperative data will be collected on the following source documents:

1. Inclusion/Exclusion Criteria
2. Demographic Evaluation
3. Physical Exam
4. Forgotten Joint Score (FJS-12)
5. Oxford Knee Score
6. UCLA Activity & Satisfaction Survey
7. Protocol Deviation (as applicable)
8. Study Completion (as applicable)

H. Surgical Technique

Standard operative procedures will be followed and all surgical procedures will be performed under aseptic conditions. Investigators will implant all commercially available *NexGen* TM Tibia implants and any other compatible products in compliance with corresponding labeling requirements and in accordance with appropriate surgical technique(s), found on www.zimmerbiomet.com. *NexGen* TM Tibia implants in this study must be implanted cementless, without the use of autograft bone paste slurry.

I. Surgical and Immediate Post-Surgical Data Collection

Surgical and immediate post-surgical data will be collected on the following source documents:

1. Surgical & Discharge Information
2. Physician Assessment of Postop Radiographs
3. Adverse Event Report (as applicable)
4. Protocol Deviation (as applicable)
5. Study Completion (as applicable)

Post-surgical management for study subjects will follow the investigator's standard of care for patients undergoing total knee arthroplasty (e.g. prophylactic antibiotic therapy, prevention of deep vein thrombosis, prevention of pulmonary embolism, etc.). Post-surgical rehabilitative therapy will be as prescribed by the investigator.

J. Postoperative Follow-up Data Collection

Postoperative follow-up clinical evaluations will be conducted at the following visit intervals:

Clinical Interval	Interval Window in Days Postop*	Approximate Window in Weeks or Months Postop
6 weeks	28 to 56 days	± 2 weeks
6 months	151 to 214 days	± 1 month
1 year	333 to 396 days	± 1 month
2 years	669 to 791 days	± 2 months

*Visit(s) outside of window will be determined based on Days Postop

Postoperative follow-up clinical data will be collected on the following source document forms:

1. Physical Exam
2. Physician Assessment of Postop Radiographs
3. Forgotten Joint Score
4. Oxford Knee Score
5. UCLA Activity & Satisfaction Survey
6. Adverse Event Report (as applicable)
7. Protocol Deviation (as applicable)
8. Study Completion (as applicable)
9. Explanted Device Form (as applicable)

Subjects will be followed postoperatively for 2 years. Unless the study is otherwise closed, data will continue to be collected until the subject completes the study per the protocol, voluntarily withdraws from the study, is withdrawn from the study by the investigator, is lost to follow-up, undergoes revision to remove a study device, or expires. See Management of Incurrent Events (Section X, Subsection D of this protocol) for additional details. Reason(s) for study completion must be documented on the **Study Completion** form.

K. Minimization of Subjects Lost to Follow-up

Subject follow-up is extremely important for the conduct of a clinical study, and the expectation is to maintain the highest possible rate of follow-up compliance throughout this study. During the informed consent process and at each follow-up interval, subjects should be counseled on the importance of completing future study follow-up intervals.

L. Radiographic Definitions and Methods

All postoperative radiographs will be evaluated by the Investigator and documented using the **Physician Assessment of Postop Radiographs**. An **Adverse Event Report** must be completed for findings identified as an adverse event.

It is the Investigator's responsibility to review radiographs for image quality during the subject's clinical visit and prior to uploading into the image collection service. Radiographic images must show an orthogonal view of the tibial implant interface. If the Sponsor determines a radiograph is of poor quality, then the site must reschedule the subject for additional radiographs.

1. Required radiographic views

Radiographic Interval	Interval Window	Required Radiograph
Immediate Postop	Pre weight-bearing	AP and Lateral
6 weeks	± 2 weeks	AP and Lateral
6 months	± 1 month	AP and Lateral
1 year	± 1 month	AP and Lateral
2 years	± 2 months	AP and Lateral

Both Anteroposterior (AP) and Lateral radiographs are required of the operative knee. These images should be taken according to the radiographic protocol (Appendix D). Radiographs should have similar exposure and must show the entire study device and surrounding bone. The investigative site will retain copies (hard copy/CD/digital) of all radiographs referenced for the study.

Immediate Postop Radiographs:
Fluoroscopic imaging is the optimal technique for immediate postop radiographs taken in the Operating Room. Standard films that show an orthogonal view of the tibial implant interface and taken prior to weight-bearing will also be accepted.

Follow-up Radiographs:
Required intervals include clinical follow-up visits at 6 weeks, 6 months, 1 year, and 2 years. Images must show an orthogonal view of the tibial implant interface.

2. Submission to Sponsor
All radiographs must be submitted to Sponsor via the designated image collection services. Postoperative study radiographs will be assessed by an independent radiographic reviewer.

M. Recommended Revision Procedure

See Management of Incurrent Events (Section X, Subsection D of this protocol)

X. Reporting

The management of all study data received by the Sponsor will be the responsibility of the Sponsor or its Designee. The use or disclosure of all protected health information will comply with the Health Insurance Portability and Accountability Act (HIPAA). All information will be treated with strict adherence to professional standards of confidentiality and will be filed by the Sponsor under adequate security and restricted accessibility by clinical personnel. All electronic

systems used to create, modify, maintain, or transmit study records will be validated according to 21 CFR Part 11 [2]. Reports and communications relating to study subjects will typically identify each subject only by the subject's initials, assigned study subject Case ID number, date of surgery, operative side, and date of birth. This code must be clearly linked to the patient identity and can only be decoded by the study center.

A. Prior to Initiation of the Study

1. Clinical Trial Agreement (CTA)
   A fully executed (signed by all required parties) CTA must be on file with the Sponsor prior to any investigator participating in this study.

2. Institutional Review Board Protocol Approval
   This study protocol must be submitted to and approved by the Investigator's Institutional Review Board (IRB). A copy of the IRB approval letter must be submitted to Sponsor. The letter should identify the following:
   - Protocol name and/or number
   - Date of IRB meeting (if available)
   - Date of approval
   - Date of expiration
   - Signature of IRB

3. Informed Consent
   A Sponsor-approved sample **Informed Consent Form** (Appendix A) will be provided along with the study protocol for IRB submission and approval. If the IRB requires revisions to the provided Informed Consent Form, the requested revisions must be submitted by the Investigator to the Sponsor for review and approval. Once the Sponsor has reviewed and approved the revision, the Informed Consent Form will be re-submitted to the IRB for final review and approval. A copy of the final IRB approved Informed Consent Form (ICF) must be submitted to Sponsor.

4. ClinicalTrials.gov Registration
   The Sponsor will be responsible for registering this study on www.ClinicalTrials.gov.

B. Clinical Data Collection/Submission

1. Summary of Source Document Data Collection
   Study data will be collected on source documents, which may include study-specific documents provided by the Sponsor. For subjects having bilateral knee replacement, separate source documents must be completed for each operative side.

   The following source document completion guidelines should be followed:
   - Complete carefully and accurately.
   - Complete header information consistently across all source documents for each individual study subject (when study-specific forms are used).
   - Be sure that data on the source documents match that which is entered through the electronic data capture (EDC) system.
   - Use the study subject's unique Case ID number assigned as instructed. Do

not provide information that is not requested on the source documents.
- Ensure that all fields are completed. For fields completed by the subject, efforts should be made to obtain any missing responses prior to the subject completing their visit.

2. Data Submission
Completed source documents will be submitted directly to Sponsor by electronic data capture (EDC) and submission via a method approved by Sponsor. Every effort must be made to ensure data submission to Sponsor is made within 14 days of the visit completion.

3. Quality Assurance of Data
The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the EDC and in all required reports. Data reported in EDC, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All electronic systems used to create, modify, maintain, or transmit electronic study records will be validated according to 21 CFR Part 11 [2]. The Sponsor will maintain quality control systems, in accordance with the Sponsor's policies and procedures.

C. Reporting Requirements

1. Investigator Reporting Responsibilities
The Investigator should ensure the accuracy, completeness, legibility, and timeliness of data reported to the Sponsor in accordance with this protocol. The Investigator or Designee will provide periodic reports to their IRB as required to maintain IRB approval throughout the study, and will provide any required final reporting to the IRB upon study completion/termination. A copy of all IRB re-approval letters must be submitted to the Sponsor. If the IRB terminates or suspends its approval of the study, the Investigator or Designee will suspend study-related activities and will promptly notify the Sponsor. The Investigator should also promptly provide written reports to the Sponsor and the IRB regarding any changes significantly affecting the conduct of the study, and/or increasing risk to the subjects.

2. Retention of Records
Study records must be retained by the Investigator or Designee for a minimum of 2 years from the Investigator's study termination date, or per applicable regulatory and/or IRB requirements (whichever time period is greater). Measures shall be taken to prevent accidental or premature destruction.

D. Management of Incurrent Events

1. Failure to Obtain Informed Consent
Study data will not be collected until the Informed Consent Form has been properly executed. If a candidate does not wish to participate (does not sign and date the Informed Consent Form), data for that candidate will not be collected for this study.

2. Reporting and Documentation of Medical Events, Adverse Events and Adverse Device Effects

   Adverse Events, Serious Adverse Events, Adverse Device Effects, and Serious Adverse Device Effects will be documented on the **Adverse Event Report** throughout this study, including information on the date of onset, treatment and resolution, as well as assessment of both the seriousness and the relationship to the study device. The outcome of complications will be documented and changes in outcome are to be updated during the course of the study. In case of early termination of this study, further follow-up of the subject shall proceed according to the hospital's standard procedure.

   Device Deficiencies that did not lead to an adverse event but could have led to a medical occurrence if suitable actions had not been taken, if intervention had not been made, or if circumstances had been less fortunate, shall be reported to the Sponsor as soon as possible, as well.

   See Section X, Subsection E of this protocol for additional information regarding adverse event classifications. All medical events, regardless of classification, are required to be reported on the **Adverse Event Report**. The completed **Adverse Event Report** must be submitted to the Sponsor in a timely manner. The Investigator or Designee will also promptly provide the Sponsor with any additional requested information required for the Sponsor to comply with regulatory requirements. If applicable per their reporting requirements, the Investigator or Designee will also report applicable adverse event(s) to their IRB.

3. Revision

   Study subjects will be study completed for any revision, regardless of the component being revised. In the event that removal of one or more of the implanted knee components is necessary, the Investigator will determine the best treatment and/or revision method for the subject.

   Prior to revision surgery, the Investigator or qualified Designee must document radiographic findings on the **Physician Assessment of Postop Radiographs**.

   Once the revision surgery has been completed, the Investigator or qualified Designee must complete an **Adverse Event Report** as well as a **Study Completion** form terminating the subject from the study. For the study completion status, select "Study Prosthesis Removed".

   All explanted device information must be documented on an **Explanted Device Form**. In addition, all explanted devices must be returned to Zimmer Biomet using the **Explant Procedure** (Appendix F).

4. Investigator Withdrawal

   The Investigator can choose to withdraw a subject from the study if the subject no longer meets study inclusion/exclusion criteria. The reason for the Investigator's withdrawal of the subject must be documented on the **Study Completion** form.

5. Subject Withdrawal
   Study subjects may choose to withdraw from the study at any time, for any reason. If possible, a final evaluation will be completed for any subject who no longer wishes to participate in the study. The reason for the subject withdrawal must be documented on the **Study Completion** form.

6. Lost to Follow-up
   A study subject will be considered lost to follow-up after they have missed a visit and attempts to locate and evaluate the subject using the procedure outlined below have failed. All attempts to contact the subject are to be documented in the subject's medical record and on the **Study Completion** form. Missed visit(s) also must be documented using the **Protocol Deviation** form, unless the visit is retrospective. The first three contact attempts should be made by telephone, with additional attempts as outlined in the following table:

If	Then
a response is not received after three (3) phone calls	the Investigator or Designee should send a letter to the subject explaining the follow-up agreement per the Informed Consent, and requesting a response from the subject.
all attempts to contact the subject are unsuccessful or the subject is contacted and chooses to withdraw from the study	a **Study Completion** form will be completed and will specify the reason the subject is no longer participating in this study.

7. Protocol Deviations
   Investigators should not deviate from the study protocol. If a protocol deviation does occur, the deviation must be documented on the **Protocol Deviation** form and submitted to the Sponsor. If applicable per their reporting requirements, the Investigator or Designee will also report applicable protocol deviations to their IRB.

8. Study Termination
   Study subject participation is expected to end upon completion of the subject's 2 year follow-up visit unless the subject voluntarily withdraws from the study, is withdrawn from the study by the Investigator, is lost to follow-up, undergoes revision to remove a study device, or expires. Reason(s) for study completion must be documented on the **Study Completion** form.

   If the Sponsor decides to terminate the study early, the Sponsor will inform the Investigators of the reason for early study termination. It is the responsibility of the Investigators to inform their IRB as applicable according to local and national laws/regulations.

9. Modification of the Protocol
   All amendments to this clinical protocol shall be agreed to by the Sponsor and be recorded with a justification for the amendment prior to implementation. Approval of

the applicable IRB must be obtained prior to implementation, if required according to the local and/or national laws/regulations.

E. Medical Events/Adverse Events Definitions and Classifications

An adverse event is any unfavorable or unintended sign, symptom, or disease associated with the use of the study device, whether or not related to the device. Adverse event is synonymous with complication or medical event. All medical events, regardless of classification, are required to be reported on the Adverse Event Report case report form. The completed **Adverse Event Report** must be submitted to the Sponsor in a timely manner. The Investigator or Designee will also promptly provide the Sponsor with any additional requested information required for Sponsor to comply with regulatory requirements. If applicable per their reporting requirements, the Investigator or Designee will also report applicable adverse event(s) to their IRB.

1. Classification of the Event

   Adverse Event (AE) [1]:

   An Adverse Event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

   Note 1: This definition includes events related to the investigational medical device or the comparator.

   Note 2: This definition includes events related to the procedures involved.

   Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

   Serious Adverse Event (SAE) [1]:

   A Serious Adverse Event is any adverse event that

   a. led to death
   b. led to serious deterioration in the health of the subject, that either resulted in:
      1. a life-threatening illness or injury, or
      2. a permanent impairment of a body structure or a body function, or
      3. in-patient or prolonged hospitalization, or
      4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
   c. led 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 protocol, without serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE) [1]:
An Adverse Device Effect is an adverse event related to the use of a medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the medical device.

Serious Adverse Device Effect (SADE) [1]:
A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

The Sponsor is responsible for determining the final classification of adverse events.

If an Unanticipated Serious Adverse Device Effect (USADE) is identified it will be promptly reported to concerned Investigators and regulatory authorities as required by applicable regulatory requirements. If applicable per their reporting requirements, the Investigator or Designee will report the USADE to their IRB.

2. 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 event interferes considerable 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.

3. 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.

Medical Device Information Reporting
For any adverse event with a relation to device of "Uncertain", "Probably" or "Definitely", a **Medical Device Reporting Information Form** (MDRIF, Appendix E) must be completed and submitted to the Study Manager within 7 days. Other required supporting documentation that should be sent with the MDRIF:

- All subject x-rays
- Operative notes
- A summary detailing the subjects postoperative physical therapy regimen
- Subject activity level at the time the event occurred.

4. Outcome Definitions

The outcome is in relationship to the Adverse Event, not the treatment rendered for the event (if any).

Resolved:
The adverse event has been resolved and/or no further treatment is required to treat the reported condition or illness.

Tolerated:
The adverse event will most likely never be resolved. The subject "tolerates" the illness or condition as a matter of life.

Pending:
Treatment or diagnostic studies were prescribed for the adverse event and the outcome of the adverse event is not yet known.

Study Withdrawal:
Due to the adverse event, the subject was withdrawn from the study.

Device Revision/Removal:
The adverse event resulted in the removal of a study device.

Death:
The outcome indicates the subject died as a direct result of the reported adverse event.

Reoperation of Affected Joint:
The adverse event resulted in reoperation of the study joint, but the reoperation did not include removal of a study device.

5. Collection Approach
   The type of approach taken to collect adverse event information, whether systematic or non-systematic.

   Systematic:
   Based on checklists, questionnaires, or tests

   Non-Systematic:
   Based on spontaneous reporting and recording

F. Monitoring of the Study

Prior to initiating the clinical study, the Sponsor will conduct a site initiation visit to ensure the Investigator(s) and study staff understands the study protocol and requirements and have adequate time and resources to implement and conduct the study. Prior to study initiation, the Investigator must have a fully executed CTA and IRB approval of the study protocol and the study Informed Consent.

During the course of the study, the Sponsor will conduct periodic central monitoring and maintain contact with the study staff to monitor compliance and evidence of adverse events, in accordance with the Sponsor's policies and procedures. The Sponsor will address any identified non-compliance with the executed CTA, study protocol, and applicable regulatory requirements.

If onsite monitoring visit(s) are deemed appropriate by the Sponsor, the Investigator will permit representatives of the Sponsor's monitoring team to have direct access to inspect all source data/documents, study documents/binders, corresponding sections of study subject medical/hospital records, and any other documents relevant to the study. All Sponsor visits (including site initiation) will be documented using the **Monitoring Visit Log** (Appendix C).

XI. Risk Analysis

This post-market clinical study is classified as minimal risk [2] and there are no anticipated risks specific to study participation other than the potential loss of confidentiality. There are no experimental procedures in this study, and participation in this study is not anticipated to affect the medical treatment of enrolled subjects.

The *NexGen* knee components being studied are post-market, non-investigational devices cleared by the FDA via 510(k). The subjects included in this study could receive the devices without participating in the study.

- *NexGen* TM Monoblock Tibia (K012866, K020295, and K031462)
- *NexGen* TM Modular Tibia (K072160)

When used in accordance with product labeling, the risks associated with the use of *NexGen* cementless knee components are similar to those of standard, metal-on-polyethylene cementless knee systems used for the same clinical indication or purpose. These risks are categorized below as either general surgical risks or risks associated with a cementless total knee arthroplasty procedure/study device. Unanticipated adverse events can also occur.

A. General Surgical Risks

General surgical risks and post-operative adverse events can occur with any surgery and include, but are not limited to:

- Anesthetic complications/reactions
- Bleeding and/or excessive blood-loss
- Transfusion reaction
- Chronic Pain
- Post-operative infection
- Vascular injury
- Delayed wound healing
- Deep vein thrombosis (DVT)
- Nerve injury
- Death

B. Risks Associated with Cementless Total Knee Arthroplasty/Study Device

Potential adverse events associated with cementless total knee arthroplasty include, but are not limited to:

- Loosening or fracture/damage of the prosthetic knee components or surrounding tissues.
- Dislocation and/or joint instability.
- Malalignment of the prosthetic knee components.
- Bone fracture or nerve damage.
- Swelling or infection.
- Leg length discrepancies.
- Poor range of motion.
- Pain.
- Venous thromboembolic disease.
- Inflammation.
- Metal sensitivity.
- Corrosion of metal components (the significance and long-term implications are uncertain and await further clinical evidence and evaluation).
- Wear debris can initiate osteolysis which may result in loosening of the implant.

Minimization of Risk

Complications and/or failure of prosthetic implants are more likely to occur in patients with unrealistic functional expectations, heavy patients, physically active patients, and/or with patients who fail to follow through with the required rehabilitation program. Physical activity or trauma can result in loosening, wear, and/or fracture of the implant. The patient must be counseled about the capabilities of the implant and the impact it will have on his or her lifestyle. The patient must be instructed about all postoperative restrictions, particularly those related to occupational and sports activities and about the possibility that the implant or its components may wear out, fail or need to be replaced. The implant may not last the rest of the patient's life, or any particular length of time. Because prosthetic implants are not as strong, reliable, or durable as natural, healthy tissues/bones, all such devices may need to be replaced at some point.

XII. Statistical Considerations

Performance of the commercially available *NexGen* TM Monoblock Tibia and *NexGen* TM Modular Tibia used in primary cementless tibia total knee arthroplasty will be evaluated for radiographic parameters, pain and function, and survival of the device. Data collected in this study will be summarized descriptively and descriptive summaries will be the basis of any study reports issued. These summaries may be used for interim study reports and may also be used to support regulatory submissions, presentations, and/or publications. Additional surgical technique and instrumentation data may be collected and evaluated.

A. General Statistical Methods

Statistical methodology will consist of summarizing collected data descriptively. Categorical data (e.g., gender or race) will be summarized using counts and percentages, and 95% Confidence Interval (CI), over the time periods of interest. Continuous data, such as age, will be summarized by using means, medians, standard deviation, minimum, maximum, and 95% CI over the time periods of interest. Implant survival and return to function will be summarized using a Kaplan-Meier method and presented with rates (as percentages) and confidence intervals.

B. Sample Size

A minimum of 132 subjects are to be enrolled in this study, with approximate equal distribution of at least 66 *NexGen* TM Monoblock and 66 *NexGen* TM Modular subjects. The *NexGen* TM Monoblock Tibia and *NexGen* TM Modular Tibia are considered 2 single-arms being analyzed separately. Sample size is based upon 6 to 10 sites enrolling between 22 to 30 subjects per site.

Based on NexGen's expected success rate of 98% at two years on the primary endpoint and using a 10% non-inferiority margin against a 98% performance goal, 57 subjects are required to achieve 80% power to test non-inferiority. 57 subjects also allow the Sponsor to control the Type-1 alpha error at 0.05. Assuming a 12% loss to follow-up over 2 years, approximately 66 subjects need to be enrolled for each single arm.

XIII. References

[1] ISO 14155:2011(E). Clinical investigation of medical devices for human subjects – Good clinical practice.

[2] US Food and Drug Administration. eCFR – Electronic Code of Federal Regulations Title 21. Retrieved April 25, 2017, from https://www.ecfr.gov/cgi-bin/text-idx?SID=e0cb187b56d9cb0279bb080f88b8121d&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl.

[3] Fricka KB, Sritulanondha S, McAsey CJ. To Cement or Not? Two-Year Results of a Prospective, Randomized Study Comparing Cemented Vs. Cementless Total Knee Arthroplasty (TKA). *J Arthroplasty*. 2015 Sept;30(9 Suppl):55-58.