PROTOCOL TITLE: **A PROSPECTIVE, RANDOMIZED STUDY COMPARING THE SURVIVAL FOR X-3 POLYETHYLENE TO N2VAC POLYETHYLENE WHEN USED WITH THE TRIATHLON POSTERIOR STABILIZED (PS) TOTAL KNEE SYSTEM**

PRINCIPAL INVESTIGATOR: **MATTHEW P. ABDEL, M.D.**

SUB-INVESTIGATORS : **HAROLD I. SALMONS, M.D.**

DIRK R. LARSON, M.S.

MICHAEL J. STUART, M.D.

MARK W. PAGNANO, M.D.

MARK J. SPANGEHL, MD

HENRY D. CLARKE, MD

CEDRIC J. ORTIGUERA M.D.

INVESTIGATOR ADDRESS: **MATTHEW P. ABDEL, M.D.**

MAYO CLINIC

200 FIRST ST. SW

ROCHESTER, MN 55905

SUMMARY

A prospective, randomized, single-blinded clinical trial is proposed to compare Stryker Orthopaedics N2Vac Polyethylene to their X3 Polyethylene when used with the Triathlon Posterior Stabilized (PS) total knee system. This is a fixed-bearing knee intended for use in patients undergoing cemented total knee arthroplasty. The devices to be used are both FDA approved via 510k clearance.

A total of 572 cases (286 per group) will be entered. Each patient will be assessed pre-operatively and post-operatively at three months and two, five, seven and ten years. The primary endpoint will be the revision rate at ten years. This outcome will be evaluated using event rates analysis assuming a Poisson distribution. Additional endpoints, including the instance of mortality, revision surgery, deep vein thrombosis, pulmonary embolus, neurovascular complication, and infection will be evaluated in the same manner. Other outcome measures incorporated in the Knee Society Clinical rating scale will undergo appropriate generalized linear regression for the type of outcome involved.

PURPOSE

The primary aim of the study is to compare the survivorship of two types of polyethylene (conventional N2Vac and highly cross-linked X3) used in a fixed-bearing total knee system in patients undergoing cemented total knee arthroplasty. These results will be measured through radiographs at each post-operative interval with an independent radiograph review being performed after all patients have reached 7 and 10 year follow-up. Secondary results will also be collected and will focus on disease-specific (Knee Society Scores), global (SF-12), and outcome measures. Radiographic results consisting

of standing anteroposterior, lateral and Merchant views of the surgical knee will be recorded and analyzed. Completion of the initial investigation will occur at the 10-year interval after the last enrolled patient.

INTRODUCTION

Pain, weakness, instability, and progressive dysfunction are the hallmarks of arthritis of the knee. Total knee replacement may frequently be the only therapeutic intervention to provide adequate improvement in pain and function. Fixed bearing knees have a long track record of clinical success but the issue of polyethylene wear resulting in debris that leads to osteolysis has been the limitation of the survivorship of these implants. Highly cross-linked polyethylene has been used in hips for over 7 years with excellent clinical results. However the use of first-generation of highly cross-linked polyethylene in the knee has been avoided over concerns of the ability of highly cross-linked polyethylene to withstand shear forces across the tibia.

METHODS AND MATERIALS

Study Design

This will be a prospective, single-blinded, randomized clinical trial. A physician's assistant will supervise the running of the study and evaluate the patients. The randomization will be provided through a password-protected computer program developed by Mayo Clinic Division of Biostatistics personnel that can be accessed at any surgical computer terminal by the research assistant. Patients will be blinded as to which

polyethylene tibial insert and patella they have received, provided they do not insist on being informed, or unless it becomes medically necessary to do so.

Randomization of the Study Patients

In order to assign patients to specific treatment groups in an unbiased manner, randomization will occur prior to surgery. After the patient has met the entrance criteria, and given full informed consent to participate in the study, they will be assigned to the treatment group. The randomization will be stratified by variables with potential confounding effects on the outcomes of interest. Specifically, patients will be stratified by gender (male / female), Body Mass Index category (<25.0 / 25.0-29.9 / ≥30) and age group (21-55 / 56-85). Within each stratum, subjects will be assigned to one of the two treatment groups using a computerized dynamic allocation program. Patient randomization will be performed just prior to surgery.

Sample Size/Inclusion Criteria

Five hundred seventy-two (572) patients will be recruited into the study; 286 receiving N2Vac polyethylene and 286 receiving X3 polyethylene.

Surgical Technique

All procedures will be performed by one of nine knee arthroplasty surgeons (MEC, ADH, TMM, MWP, JSS, MJS, CJO, HDC, MJS). The femoral, tibial and patellar components will be cemented. The patellar components will be all-polyethylene.

Hospitalization

Patients will be admitted to the hospital on the day of their surgery, unless medical problems dictate earlier admission. Hospitalization of 3 to 5 days is routine for these

patients, although complications may prolong this. These will be recorded on the data collection forms. An extension splint will not be used following surgery and no pillows are to be used under the knee. Continuous passive motion will be used according to the individual surgeon's discretion as part of the postoperative management. The patient will receive one preoperative dose and two postoperative doses of IV antibiotics separated by a 6 to 8 hour period. All patients will receive appropriate anticoagulation for deep venous thrombosis prophylaxis at the individual surgeon's discretion.

Post-Op Physical Therapy

Both treatment groups will have similar postoperative care. Structural physical therapy will begin the day after surgery and continued during the hospitalization. A home therapy program will be given to the patient.

a. Initial Post-op Day 1, use of walker or personnel to assist with transfer from bed to chair.
b. Active ROM to begin within first 24 hours postop.
c. Weight bearing status and progression as tolerated.

Progression

- Progress ambulation from walker or crutches to a cane as tolerated
- Post-Op Day 1 – commence ice and exercises as per exercise attached. May include patellar mobilizations, massage to reduce swelling.
- CPM initiated (at the individual surgeon's discretion) on the day after surgery as tolerated and discontinued at dismissal from hospital.

- Patients should be encouraged to maximize independent ambulation and increase distance ambulated daily

Discharge Criteria

- Independent and safe using a walker or crutches for ambulation and satisfactory pain control.

Radiographic Parameters

Standing alignment, lateral, and Merchant (45 degrees of flexion) radiographs will be obtained preoperatively, immediately postoperatively, and three months, two years, five years, seven years, and ten years after surgery. An independent reviewer will evaluate the radiographs for radiolucent lines, component position and alignment after all patients have completed the seven-year and ten-year visit.

Study Procedures

Data Collection (obtained via a blinded research assistant)

Visit #1	Preoperative: Consent and initial data acquisition: Knee Society Clinical Rating Score, SF-12, Radiographs of the knee (standing alignment, lateral and Merchant view at 45° of knee flexion)
Visit #2	Three months: Radiographs of the knee (standing alignment, lateral and Merchant view at 45° of knee flexion); Knee Society Clinical Rating Score, SF-12. These questionnaires can be obtained in-office, by phone or by mail. While it is preferred that the visit occur in the clinic, if the participant is not returning they will still be asked to complete the study questionnaires.

Visit #3	Two years: As above #2. . These questionnaires can be obtained in-office, by phone or by mail. While it is preferred that the visit occur in the clinic, if the participant is not returning they will still be asked to complete the study questionnaires.
Visit #4	Five years: As above. These questionnaires can be obtained in-office, by phone or by mail. While it is preferred that the visit occur in the clinic, if the participant is not returning they will still be asked to complete the study questionnaires.
Visit #5	Seven years: As above. These questionnaires can be obtained in-office, by phone or by mail. While it is preferred that the visit occur in the clinic, if the participant is not returning they will still be asked to complete the study questionnaires.
Visit #7	Ten years: As above. These questionnaires can be obtained in-office, by phone or by mail. While it is preferred that the visit occur in the clinic, if the participant is not returning they will still be asked to complete the study questionnaires.

Measurement Tools

Knee Society Clinical Rating Score

This is a clinical standard for rating efficiency of total knee replacement. It is a disease-specific test, which has been validated and is widely used. These questionnaires can be obtained in-office, by phone or by mail. While it is preferred that the visit occur in the clinic, if the participant is not returning they will still be asked to complete the study questionnaires.

SF-12

This self-administered questionnaire has been validated for measuring and monitoring health status in large group studies. These questionnaires can be obtained in-office, by phone or by mail. While it is preferred that the visit occur in the clinic, if the participant is not returning they will still be asked to complete the study questionnaires.

Complications/Lost to Follow-up Form

Any serious complication, which occurs relating to the device, will be documented. Sepsis, embolism, failure of primary wound healing, hemorrhage, prosthesis loosening, skin necrosis, hematoma, device failure or fracture are possible complications. If for any reason a patient is lost to follow-up (will not return for office visits or complete and return mailed study questionnaires) there must be a completed form to indicate this event.

Financial Complications

None

Timetable

The estimated time required to enroll 572 cases is three years.

Medical Device

All study devices are FDA-approved.

PARTICIPANT POPULATION

Eligibility Criteria

Inclusions:

1. Subjects willing to sign the informed consent.
2. Subjects able to comply with follow-up requirements including post-operative weight bearing restrictions and self-evaluations.
3. Male and non-pregnant female subjects ages 21-85 years of age at the time of surgery.
4. Subjects requiring a primary total knee replacement.
5. Subjects with a diagnosis of osteoarthritis (OA), traumatic arthritis (TA), or avascular necrosis (AVN).
6. Subjects with intact collateral ligaments as determined by the surgeon investigator.

Exclusions:

1. Subjects with inflammatory arthritis.
2. Subjects with a history of total or unicompartmental reconstruction of the affected joint.
3. Subjects that have had a high tibial osteotomy or femoral osteotomy.

4. Subjects with neuromuscular or neurosensory deficiency, which would limit the ability to assess the performance of the device.
5. Subjects with a systemic or metabolic disorder leading to progressive bone deterioration.
6. Subjects that are immunologically compromised, or receiving chronic steroids (>30 days).
7. Subjects bone stock is compromised by disease or infection that cannot provide adequate support and/or fixation to the prosthesis.
8. Subjects with knee fusion to the affected joint.
9. Subjects with an active or suspected latent infection in or about the knee joint.
10. Subjects that are prisoners.

Recruitment

The investigator or the research assistant will carry this out. The study will be described to the patient in detail, and a consent form, clearly stating the background and reasoning, will be given to the patient. A consent form will be signed by the patient and by a study person authorized to obtain consent. One copy will be go with the participant as stated, a second copy will go into the patient's medical record, and the original consent will be kept in the patient's study folder.

Competency

Study participants must be able to give informed consent.

Gender and Racial/Ethnic Distribution

No gender or racial/ethnic group will be intentionally excluded from this study.

RISKS

Participation in this study, involving FDA-approved devices, poses no increased risk to patients undergoing total knee replacement surgery. With any knee replacement, there is a possibility that the prosthesis will need to be removed and replaced and that the procedure may involve unforeseeable risks. Some of the known risks include: failure to achieve firm attachment of the implant to the bone, fracture of bone during implantation, infection, deep vein thrombosis, neurovascular injury, wound problems, extensor mechanism problems, and anesthetic problems. In a minority of cases, the knee prosthesis will loosen over years of use and pain and decreased mobility will occur.

STATISTICAL METHODS AND REVIEW STATEMENT

Primary Efficacy Parameters

The primary efficacy parameter is the revision rate for total knee arthroplasty. The key time point is ten years post-surgery.

Secondary Efficacy Parameters

The secondary efficacy parameters include:

Active flexion, Passive flexion, Active extension, and Passive extension ROM at the 2, 5, 7 and 10-year visits.

KSS pain and motion scores at the 3 months, 2, 5, 7 and 10-year visit.

SF-12 scores at the 3 months, 2, 5, 7 and 10-year visit.

Radiographic success/failure at the 3 months, 2, 5, 7 and 10-year visits.

Radiographic failure is defined as a score of 10 or greater according to the Knee Society Rotenographic Scoring System, regardless of symptoms. A migrating or shifting prosthesis with or without the disappearance of radiolucent lines is also a failure regardless of the score.

Primary Efficacy Hypothesis

The primary efficacy hypothesis will be a joint superiority/non-inferiority hypothesis.

The superiority hypothesis is that the *relative risk* of revision at 10 years post-surgery in the group of patients randomized to the Triathlon CR Total Knee System using the X3 polyethylene relative to the group of patients randomized to the Triathlon CR Total Knee System using N2Vac will be less than 1.0.

The non-inferiority hypothesis is that the *relative risk* of revision at 10 years post-surgery in the X3 polyethylene group relative to the N2Vac group will be less than 1.2. In other words, the X3 polyethylene group will demonstrate a *relative* increase in the 10-year revision rate no greater than 20% compared to the N2Vac group.

Formally the superiority null and alternative hypotheses are:

$H_{S,O}$: $\pi_{X3}/\pi_{N2Vac} \geq 1.0$, and

$H_{S,A}$: $\pi_{X3}/\pi_{N2Vac} < 1.0$, where π_{X3} is the ten-year revision rate in the Triathlon CR Total Knee System group using the X3 polyethylene and π_{N2Vac} is the ten-year revision rate in the Triathlon CR Total Knee System group using the N2Vac.

The non-inferiority null and alternative hypotheses are:

$H_{NI,O}$: $\pi_{X3}/\pi_{N2Vac} > 1.2$, and

$H_{NI,A}$: $\pi_{X3}/\pi_{N2Vac} \leq 1.2$, where π_{X3} and π_{N2Vac} are defined as above.

Secondary Efficacy Hypothesis

For the secondary efficacy parameters (when data is available), a non-inferiority hypothesis will be tested at each scheduled follow-up visit, similar to the primary efficacy hypothesis.

In addition, a comparison of the scores at each post-surgery visit with baseline (i.e., improvement scores) will be tested to see if any improvement is seen for each parameter and time point.

For categorical secondary parameters (i.e., radiographic success/failure, subsidence and radiolucency), the non-inferiority alternative hypothesis is that the risk in the X3 polyethylene group is not Δ_0% worse relative to the N2Vac treated group within the period from surgery to the scheduled follow-up visit. Formally the non-inferiority null and alternative hypotheses are:

$H_{NI,O}$: $\pi_{X3}/\pi_{N2Vac} > \Delta_0$, and

$H_{NI,A}$: $\pi_{X3}/\pi_{N2Vac} < \Delta_0$, where π_{X3} is the rate in the Triathlon CR Total Knee System group using the X3 polyethylene, π_{N2Vac} is the rate in the Triathlon CR Total Knee System group using the N2Vac, and Δ_0 is the equivalence limit difference (Δ_0).

For continuous secondary parameters (i.e., ROM, KSS, SF12), the non-inferiority alternative hypothesis is that the mean using the X3 polyethylene is not Δ_0 worse than the mean using the N2Vac treated group within ten years. Formally the non-inferiority null and alternative hypotheses are:

$H_{NI,O}$: $\mu_{X3} \geq \mu_{N2Vac} + \Delta_0$, and

$H_{NI,A}$: $\mu_{X3} < \mu_{N2Vac} + \Delta_0$, where μ_{X3} is the mean in the Triathlon CR Total Knee System group using the X3 polyethylene, μ_{N2Vac} is the mean in the Triathlon CR Total Knee System group using the N2Vac, and Δ_0 is the equivalence limit difference (Δ_0)..

The equivalence limit differences are as follows.:

Parameter	Equivalence Limit Difference (Δ_0)
Range of Motion (ROM)	10 degrees
KSS pain and motion	10%
SF-12	10%
Radiographic success/failure	No complete radiolucent lines
Subsidence and Radiolucency	No component subsidence

In addition, for the continuous parameters, a comparison of the scores at each post-surgery visit with baseline (i.e., improvement scores) will be tested to see if any improvement is seen for each parameter at each time point That is, the formal hypothesis to be tested is that the difference is zero. This is tested by:

$H_{I,O}$: $\mu_{i,j} - \mu_{i,0} = 0$, and

$H_{I,A}$: $\mu_{i,j} - \mu_{i,0} \neq 0$, where $\mu_{i,j}$ is the parameter's true mean at nominal visit j for treatment group i, where i is either X3 or N2Vac, and $\mu_{i,0}$ is the corresponding baseline parameter's true mean for treatment group i.

Safety

Primary Safety Parameters

The primary safety parameter is the incidence of patellar fracture, dislocation, subluxation and wear.

Secondary Safety parameters

The secondary safety parameter is the incidence of all other device related adverse events.

Primary Safety Hypothesis

The incidence of patellar fracture, dislocation, subluxation and wear is the same in the Triathlon CR group as in other commercially available knees.

Secondary Safety Hypothesis

The incidence of all other device related adverse events is the same in the Triathlon CR group as in other commercially available knees.

Missing Data

Scores for missing SF-12 data will be imputed using the SF Health Outcomes Scoring Software. Both raw and imputed results will be reported. The imputed values will be analyzed.

Statistical Methodology

Data Summary

All data entry and analysis will be done by the Mayo Clinic Division of Biostatistics. The following is a detailed proposal of statistical analyses planned for data collected during the study. In general, data will be summarized by treatment group and nominal study visit, where applicable.

For parameters represented by continuous variables (e.g., ROM), the summaries will consist of the mean, median, standard deviation, minimum, and maximum values. Both the actual values at each nominal visit and the improvement from baseline at each post-baseline visit for each treatment group and their difference will be presented with its 95% confidence intervals. The improvement from baseline will also present the corresponding paired t-test p-values.

For categorical variables (e.g., subsidence), the number of events, person-years of follow-up, and the corresponding event rates with 95% confidence intervals will be presented. In addition, the rate ratios (relative risk) of the treatment groups along with 95% confidence intervals will be presented.

Descriptive statistics and statistical comparisons for important demographic, efficacy, and safety variables will be provided in tables. All data collected on the case report forms will be provided in data listings, which will be sorted by treatment group and patient number.

Documentation of statistical analyses will be provided in a statistical appendix. All statistical analyses will be completed using SAS®, version 9 or higher (SAS Institute Inc, Cary, NC), and Splus, version 7 or higher (Insightful Corporation, Seattle, WA).

All statistical tests will be two-sided and p-values less than 0.05 will be considered significant.

Sample Size Justification

Revision rates for total knee arthroplasty are approximately 0.5% per year over the life of the knee. At ten years, this rate would be expected to be 5%. Within the Triathlon PS, X3 has been shown to reduce wear over N2Vac by up to 68%. Therefore, by assuming all revisions could be attributed to polyethylene debris the X3 can be assumed to have a revision rate of 1.6% at 10 years. Assuming that the X3 knees have a 10-year revision rate of 1.6% and that the corresponding rate in the N2Vac knees is 5.0% yields a rate ratio of 0.32 (or 3.1 for N2Vac/X3). In order to have 80% power to detect this rate ratio as being significantly different from 1.00 will require that 26 events (revisions) are observed during the 10-year follow-up period. Assuming the overall 10-year revision rate is 5%, the sample size required to observe 26 revisions is 26/0.05=520, or n=260 in each treatment group. By factoring in a 10% lost to follow-up rate within the ten-year period, the total enrollment of about 572 subjects (286 in each group) will be needed.

Interim Analyses and early Stopping Considerations

No interim analysis is planned.

Efficacy Analyses

Methods

Primary Parameter: The relative risk of revision (X3 relative to N2Vac) at ten years will be computed and a 95% confidence interval on the rate ratio computed, assuming a Poisson distribution. If the upper end of the confidence interval for the rate ratio is less than 1.0, then the superiority hypothesis will be supported. Otherwise, if the upper end of the confidence interval is less than 1.2, then the non-inferiority hypothesis will be supported. Secondary Parameters: The categorical secondary efficacy parameters will be analyzed at each nominal visit by computing the 95% confidence interval for the rate ratio (relative risk) of the groups as above. The clinically significant difference (Δ_0) is as presented on page 13 above. The continuous secondary efficacy parameters will be analyzed at each nominal visit. The 95% confidence interval on the difference between the two groups will be computed using the means, t-distribution and appropriate standard deviation. The change from baseline will also be presented and their 95% confidence interval and p-value for the paired t-test using the baseline will be presented for each nominal visit and treatment group, along with the descriptive statistics.

Patient Population

Modified Intent to Treat

A Modified Intent-to-Treat (MITT) population will be used. The analysis will include all subjects who received the Triathlon CR device. All subjects with any data will be included where possible.

Safety Analyses: The analysis of the primary and secondary safety parameters will parallel the analysis of the categorical secondary parameters.

Baseline and Demographic Analyses

The baseline and demographic analyzes will be presented using descriptive statistics only.

Potential Conflict of Interest for the Investigators

There may be a conflict of interest for some investigators of this study. All investigators who had financial interest were required to submit a Financial Disclosure form to the Conflict of Interest Board. The board approved those investigators for the purpose of this study.