Perioperative Antibiotic Prophylaxis in Patients Undergoing Elective Total Knee Arthroplasty: A prospective, randomized, open-label, controlled multi-center trial.



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1. INTRODUCTION

1.1 BACKGROUND

Total joint arthroplasty (TJA), is one of the most successful operations in modern medicine; however, it remains an expensive procedure in an era of constrained health care resources.[1-3] Arthritis affects 49.9 million Americans with 21.1 million experiencing arthritis-attributable activity limitations.[4] As these numbers are expected to increase significantly by 2030, the demand for primary total knee arthroplasties (TKA) by 673% to 3.48 million procedures/year.[5] Periprosthetic joint infection (PJI), with its disastrous implications, continues to challenge the orthopaedic community. Practicing orthopaedic surgeons continue to invest efforts to minimize surgical site infection (SSI). Kamath et al. evaluated characteristics and resource utilization associated with revision arthroplasty for PJI using the Nationwide Inpatient Sample. The authors found that PJI was the most common indication for revision total knee arthroplasty (TKA), and the third most common reason for revision total hip arthroplasty (THA).[6] Prophylactic antibiotics aim to provide protection against bacteria most likely to gain access to the surgical site during the procedure and in the perioperative period. The two most common bacteria causing contamination and subsequent deep infection in TKA are Staphylococcus aureus and coagulase-negative staphylococci.[7-9]

While antibiotic regimens for antimicrobial prophylaxis might carry different risks and side-effect profiles, e.g., hypersensitivity reactions (including anaphylaxis), acute kidney injury, and Clostridium difficile infection, there are a number of studies which validate the importance of the preoperative dose of antibiotics in decreasing periprosthetic joint infection (PJI) and surgical site infection (SSI) in total joint arthroplasty (TJA). However, there are conflicting recommendations/guidelines as to the optimal timing and the optimal duration perioperative antibiotics (Table I). The American Academy of Orthopaedic Surgeons (AAOS), the Centers for Disease Control (CDC), and SCIP guidelines recommend that prophylactic antibiotics be completely infused within one hour before the surgical incision.[10] The US advisory statement recommends that antimicrobial prophylaxis be administered within one hour before incision and discontinued within 24 hours after the end of the operation,[11] while European guidelines recommend a single dose within 30 minutes before incision.[12]

Table I.

Organization	**Recommendation**	
	Discontinue antibiotics within 24 hours	**Discontinue antibiotics after incision closure**
Surgical Infection Prevention Project 2002 [13]	✓	-
National Institute for Health and Care Excellence 2008 [14, 15]	-	✓
UK Department of Health 2011 [16]	-	✓ with exceptions$^{\epsilon}$
Royal College of Physicians of Ireland 2012[17]	Arthroplasty, head and neck surgery	✓ with exceptions*
British Orthopaedic Association 2012 [18]	✓	Debated
Musculoskeletal Infection Society 2013[19]	✓	-
American Society of Health-System Pharmacists 2013[20]	✓	Debated
North American Spine Society 2013[21]	Debated	Debated
American Academy of Orthopaedic Surgeons 2014[22]	✓	-
Society for Healthcare Epidemiology of America 2014[13]	✓	-
World Health Organization 2016[23, 24]	-	✓
South African Orthopaedic Association 2016 [25]	✓	-
American College of Surgeons 2016[26]	-	✓ with exceptions ‡
Center for Disease Control 2017[27]	-	✓

American Association of Hip and Knee Surgeons 2017[28]	✓	Not until further study
Southern Australian Advisory Group on Antibiotic Resistance 2017[29]	-	✓
Orthopaedic Trauma Association 2018[30]	✓	-
Duration of Antibiotics After Surgeries involving Implants in Orthopaedics. ǂ = Except arthroplasty, cardiac procedures, and implant-based breast reconstruction. * = except arthroplasty, head and neck surgery, implant surgery of the mandible, orthognathic surgery, complex septorhinoplasty. € = except arthroplasty.		

Recently, the Center for Disease Control (CDC) published its updated guidelines (2017) for prevention of SSI prevention that included a recommendation regarding peri-operative antibiotic prophylaxis. Based on their evaluation of the available literature, the CDC recommended that a single dose of peri-operative antibiotics be utilized for patients undergoing clean-contaminated surgical interventions, advocating for no prophylaxis after the incision is closed in the operating room [27]. This guideline encompasses several surgeries where implants are utilized, including arthroplasty, spine fusion, and fracture fixation. Furthermore, it was classified as a category IA-strong recommendation with high quality evidence [27]. However, much of the literature cited for this recommendation is based on cardiothoracic, vascular, and general surgeries, where few or no implants are utilized [27, 31]. It is important to recognize that these surgical cohort may behave differently from the orthopaedic patient population in terms of infection risk and severity of infection outcomes. Thus, analyzing the updated 2017 CDC guideline and literature used, only 6 out of the 45 studies utilized are orthopaedic studies (13%).[32-37] five of the 6 studies were published between 1987 and 1991, and one in 2006. Also, 5 of the 6 studies analyzed were conducted outside the USA (Canada, Netherlands, Italy, Spain, and Pakistan) with antibiotics not used or approved in the USA. Finally, none of the available studies were powered to detect a difference in the risk of infection. As an example, if the postoperative infection rate in orthopaedics is 1% to 2%, a cohort of 3500 patients per treatment group would be required in a single study to detect a difference between the treatments of interest.

This clinical research protocol seeks to address the lack of knowledge and Level I data around the optimal antimicrobial prophylaxis and to address the question if a single preoperative dose is enough compared to additional postoperative prophylaxis. Several smaller clinical studies have used pre- and post-intervention periods to assess the effect of antibiotic duration for surgical prophylaxis. Tang et al launched a surgical wound infection surveillance program to monitor all orthopaedic surgeries and changed the prophylactic antibiotic regimen from intravenous cefuroxime (one preoperative and 2 postoperative doses every 8 hours) to one single preoperative dose of intravenous cefazolin for all clean orthopaedic surgeries.[32] The authors of this study found no significant difference in the superficial and deep wound infection rates in 1,367 primary arthroplasties performed with a single preoperative dose of cefazolin versus 3 doses of cefuroxime. The deep wound infection rate for THA was 1.1% (95% CI, 0%-3.3%) in the cefuroxime group and 1.1% (95% CI, 0%-2.2%) in the cefazolin group (p=1.0). The deep wound infection rate of TKA was 1.6% (95% CI, 0%-3.8%) in the cefuroxime group and 1.0% (95% CI, 0.3%-1.7%) in the cefazolin group (p=0.63).121 In a retrospective review of 1,341 TJAs, Williams and Gustilo found no difference in deep infection rates between a 3 day and 1 day course of prophylactic antibiotics, but emphasized the importance of the preoperative dose, which was 2g of cefazolin.[33] Mauerhan compared the efficacy of a one-day regimen of cefuroxime with a 3-day regimen of cefazolin in a prospective, double-blinded, multicenter study of 1,354 patients treated with arthroplasty and concluded that there was no significant difference in the prevalence of wound infections between the two groups.[34] In the group treated with primary THA, the prevalence of deep wound infection was 0.5% (1/187) for those treated with cefuroxime compared with 1.2% (2/168) for those who had received cefazolin. In the group treated with a primary TKA, the rate of deep wound infection was 0.6% (1/178) for those treated with cefuroxime compared with 1.4% (3/207) for those who had received cefazolin.[34] Heydemann and Nelson, in a study of hip and knee arthroplasty procedures, initially compared a 24-hour regimen of either nafcillin or cefazolin with a 7-day regimen of the same and found no difference in the prevalence of infection. They then compared a single preoperative dose with a 48-hour regimen and again found no difference in infection prevalence. A total of 466 procedures was performed during the 4-year study. No deep infections developed in either the one-dose or 48-hour antibiotic protocol group. A deep infection developed in one (0.8%) of the 127 patients in the 24-hour protocol group and in two (1.6%) of the 128 patients in the 7-day protocol group for an overall infection rate of 0.6% (3/466). The authors recognized that as a result of the small sample sizes, the study lacked the power to compare the one dose and the more than one dose

categories.[35] In two trials, a total of 1609 patients were randomly assigned to receive 1.5 g of cefuroxime intravenously every 8 hours for a total of 16 hours (n = 1511) or 24 hours (n = 98) postoperatively versus 1600 patients given no postoperative prophylaxis. Both studies showed no difference between treatment groups suggesting that current available evidence may not support the efficacy of postoperative antibiotic prophylaxis for the prevention of surgical-site infections.[36, 37]

Antibiotics have been a critical public health tool since the discovery of penicillin in 1928, saving the lives of millions of people around the world. Today, however, the emergence of drug resistance in bacteria is reversing the miracles of the past eighty years, with drug choices for the treatment of many bacterial infections becoming increasingly limited, expensive, and, in some cases, nonexistent. The Centers for Disease Control and Prevention (CDC) estimates that drug-resistant bacteria cause two million illnesses and approximately 23,000 deaths each year in the United States alone. The Centers for Disease Control and Prevention (CDC) estimates that drug-resistant bacteria cause two million illnesses and approximately 23,000 deaths each year in the United States alone (https://www.cdc.gov/drugresistance/). The National Action Plan for Combating Antibiotic-resistant Bacteria provides a roadmap to guide the Nation in rising to this challenge. Developed in response to Executive Order 13676: Combating Antibiotic-Resistant Bacteria - issued by President Barack Obama on September 18, 2014 - the *National Action Plan* outlines steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria and addressing the policy recommendations with regard to antibiotic stewardship as outlined by the President's Council of Advisors on Science and Technology (PCAST). One of the goals of the National Action Plan is the implementation of evidence-based infection control practices can prevent the spread of resistant pathogens and questions the way surgeons use prophylactic antibiotics in the preoperative period.

1.2. RATIONALE

The scientific rationale for antibiotic prophylaxis is to inhibit or eliminate contaminating microorganisms that gain access to the surgical site during the procedure. Thus, the goal of administering preoperative antibiotics is to allow for adequate tissue (blood, soft tissue, and bone) concentrations by the time of incision. Thus, these antibiotics should exceed the minimum inhibitory concentration (MIC) for the organisms most likely to be encountered for the duration of the operation. While the role of perioperative antibiotic prophylaxis is well established, controversy exists about best clinical practice guidelines with regard to antibiotic regimen and route of administration. The results of the proposed study will be used to establish a clinical practice guidelines for antimicrobial prophylaxis in elective total joint arthroplasty.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. OVEREACHING STUDY OBJECTIVE

Despite advances in surgical care and implant technology, periprosthetic joint infections (PJI and surgical site infection (SSI) after total knee arthroplasty (TKA) represents a catastrophic complication. Administration of prophylactic antibiotics before surgery is a well-established strategy to prevent PJI and SSI. However, controversy exists regarding the choice of the antibiotic, duration of prophylaxis, optimal timing, and mode of delivery of routine antibiotic prophylaxis. Level I data with regard to prophylactic antibiotics in elective TKA is limited and identifying the correct antibiotic prophylaxis protocol can have profound and wide-reaching impact. The purpose of this study is to identify the comparative effectiveness of various perioperative strategies for antibiotic delivery as prophylaxis for PJI and SSI in elective primary TKA.

Null Hypothesis

A single dose of prophylactic antibiotic administered within 60 min before the incision is not an effective way to prevent PJI in elective primary total knee arthroplasty (TKA).

To examine the Null Hypothesis, this proposal uses a prospective, multi-center, randomized, two-arm, open label, controlled clinical study design.

2.2. SUB-HYPOTHESES & SPECIFIC AIMS

Sub-hypothesis, Specific Aim #1

The prolonged delivery (24 hours) of antibiotic prophylaxis after surgery does not further reduce the incidence of PJI in elective primary TKA.

To examine whether prolonged antibiotic prophylaxis for 24 hours (two additional doses) after surgery is needed to reduce PJI rate in elective TKA. The duration of prophylaxis in joint arthroplasty remains controversial. More recent data and clinical practice guidelines do not support prophylaxis beyond 24 hours.

Sub-hypothesis/Specific Aim #2

The presence of patient-level (age, BMI, gender, race, CCI, ASA) or surgery-level (tourniquet time, skin closure type, drain use, use of antifibrinolytic therapy) covariates have no impact on the incidence of PJI in elective primary TKA.

Since this will be a large multi-center study, the opportunity exists to prospectively examine whether certain patient-specific covariates such as age, gender, BMI, race, Charlson Comorbidity Index (CCI), American Society of Anesthesiologists (ASA) physical status score are independent predictors for PJI. In addition, this sub hypothesis will test if any of surgery-related covariates such as tourniquet use and time, approach, TXA/amicar/desmopressin use, skin closure type, antibiotic cement use, and drain use have an impact on the incidence of PJI in elective primary TKA.

3. STUDY DESIGN/METHODOLOGY

3.1. STUDY DESIGN

This is a prospective, randomized, controlled, open label, parallel two-arm design, multi-center study to compare different perioperative antibiotic administration protocols with regard to surgical site infection/periprosthetic joint infection rates in elective total knee arthroplasty.

All patients eligible for enrollment will be asked to sign a consent form prior to beginning the study. Prior to initiation of the study, research personnel will evaluate all patients to determine if their participation in the study protocol would have any possible negative interactions with their current medicinal treatments or co-morbidities. Participants will continue the use of all medications deemed necessary by their medical doctor during the study period.

After the screening process, patients who meet the inclusion criteria will be randomized to one of the study arms. Study participants will be followed for 90-days after surgery. All participating sites must randomize to study arm #1 and #2. Participating sites will be given the option to collect minimal versus expanded dataset that includes surgery-level covariates such as tourniquet time, skin closure type, drain use, use of antifibrinolytic therapy.

During the hospitalization, only basic data will be collected from the surgical procedure. This will allow for minimal interruption of clinical activities and ease burden on participating sites. The coordinating site will provide a template for surgical dictation to streamline data collection and further reduce burden on participating surgeons.

After TKA surgery, the surgical site infection occurrence will be assessed at 90-days postop. This simplifies the site adherence and facilities enrollment. SSI rates can be assessed during clinic visits, or via patient follow-up calls. Again, this should significantly reduce the burden on participating sites.

3.1.1. SAMPLE SIZE

A power analysis was performed to calculate the sample size based on a non-inferiority hypothesis test between two treatment groups, (1) single dose preoperative prophylactic antibiotic compared to (2) the current standard of care (one dose preoperative prophylactic antibiotic and two postoperative doses in the first 24 hours after surgery). A sample size of 3500 per group achieves 82.5% power to detect a non-inferiority margin difference between the treatment group proportions of 0.0075. This assumes that the reference group proportion is 0.015, and that the

treatment group proportion is 0.0225 under the null hypothesis of inferiority. The test statistic used is the one-sided Z-test (unpooled) with a significance level of 0.050. Given these numbers and taking into account a maximum 6.25% lost to follow-up or drop-outs, a total of 4000 patients will be randomized to each group for a total number of patients enrolled of 8,000. If the test for non-inferiority is significant, a test for superiority will be performed with 84.5% power to detect a 50% reduction in the event rate.

1. Numeric Results for Non-Inferiority Tests for the Difference Between Two Proportions
Test Statistic: Z-Test with Unpooled Variance
H0: P1 - P2 ≥ D0 vs. H1: P1 - P2 = D1 < D0.

				Ref.	P1|H0	P1|H1	NI Diff		Diff
Power*	**N1**	**N2**	**N**	**P2**	**P1.0**	**P1.1**	**D0**	**D1**	**Alpha**
0.82544	3500	3500	7000	0.0150	0.0225	0.0150	0.0075	0.0000	0.050

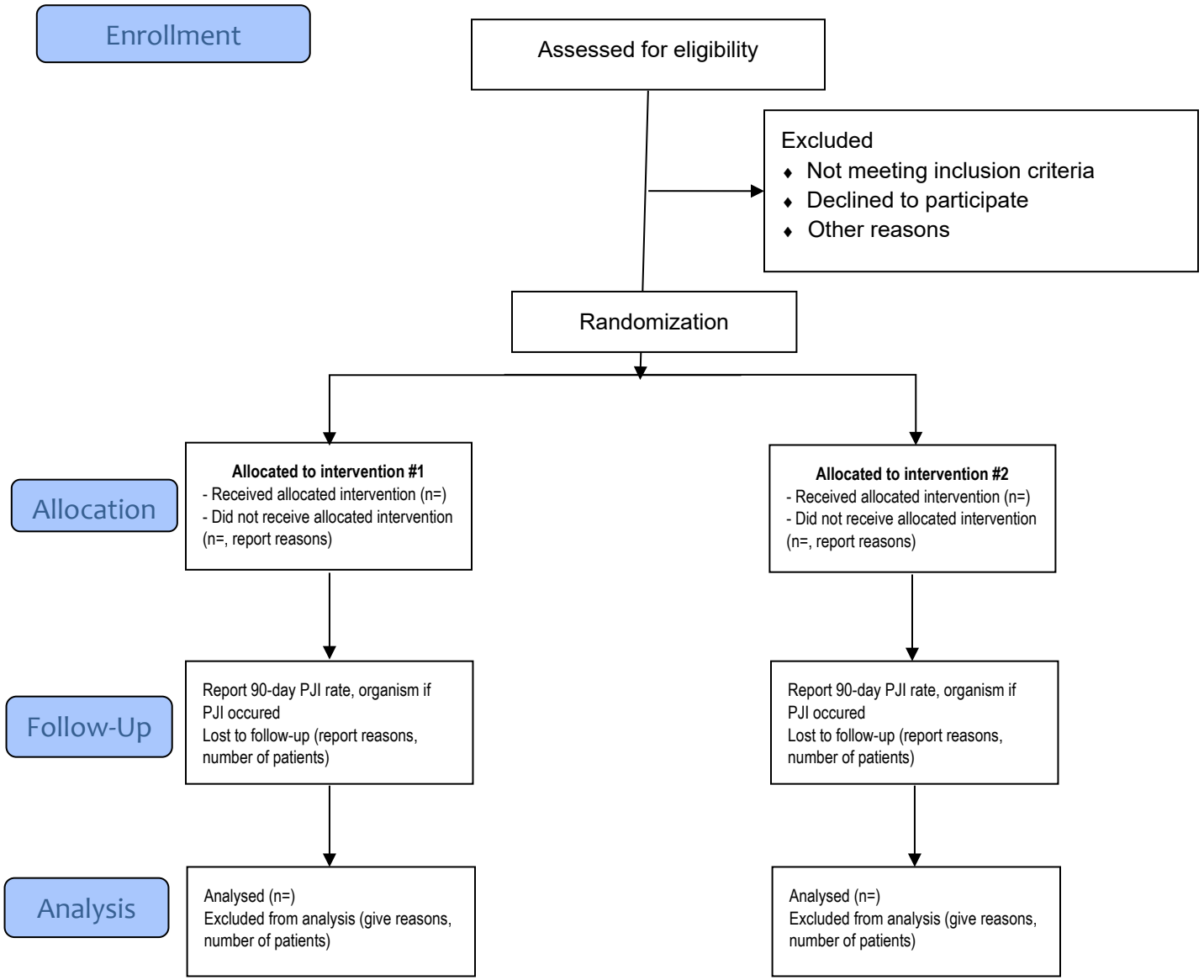
2. Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance
H0: P1 - P2 = 0. H1: P1 - P2 = D1 ≠ 0.

Power*	**N1**	**N2**	**N**	**P1**	**P2**	**D1**	**Alpha**
0.84536	3500	3500	7000	0.0150	0.0075	0.0075	0.0500

In the case that patients received the wrong number of doses compared to their randomization, data collection will proceed and decision will be made at the conclusion of the study if additional patients need to be recruited to maintain the calculated power. In addition, the obtained data (based on number of patients with this protocol violation), may be used for an unintended cross-over analysis.

3.2. STUDY DESIGN – SCHEMATIC CONSORT Flow Diagram

Perioperative Antibiotics in Total Knee Arthroplasty
CONSORT Study Flow Diagram



3.3. STUDY INTERVENTIONS & RANDOMIZATION

3.3.1. STUDY INTERVENTIONS

3.3.1.1. STUDY GROUP #1

Patients in Group #1 will receive a single weight-based dose of prophylactic cefazolin antibiotic that is administered intravenously within less than 60 minutes [38-41] prior to skin incision in elective total knee arthroplasty. No further antibiotic administration will be given.

< 120 kg – patients will receive 2 grams of cefazolin
≥ 120 kg – patient will receive 3 grams of cefazolin

Patients with documented allergy/anaphylactic reaction to penicillin or cephalosporin may receive intravenous vancomycin (15 mg/kg or <80 kg = 1gram, 80-99 kg = 1.25 grams, 100-120 kg = 1.5 grams, >120 kg = 2 grams) monotherapy or dual therapy with vancomycin (15 mg/kg or <80 kg = 1gram, 80-99 kg = 1.25 grams, 100-120 kg = 1.5 grams, >120 kg = 2 grams) and gentamicin 1.5-5 mg/kg as an alternative. [42] In addition, the use of clindamycin as an alternative is also permitted at a minimum recommended dose of 600 mg or 900 mg.

The application of **topical antibiotics (sprinkled into the wound)** such as vancomycin powder or antibiotic beads prior to wound closure in addition to standard parental peri-operative antibiotics is a protocol violation and is **not** permitted.

- Intra-operative re-dosing may be required to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug or if there is excessive blood loss (>1500 mL) during the procedure. Re-dosing of antimicrobials is recommended to occur at intervals of 1-2 times the half-life of the drug. The re-dosing intervals should be measured from the time of administration of the preoperative dose and should occur at the following intervals:

Antibiotic	Normal Renal Function	Renal Insufficiency (<30ml/min)
Cefazolin	4 hours	4 hours
Clindamycin	6 hours	6 hours
Gentamicin	No re-dosing	No re-dosing
Vancomycin	12 hours	24 hours

There should be no need to intra-operatively re-dose gentamicin or vancomycin.

3.3.1.2. STUDY GROUP #2

Patients in Group #2 will receive a single weight-based dose of prophylactic cefazolin antibiotic that is administered intravenously within less than 60 minutes [38-41] prior to skin incision in elective total knee arthroplasty. In addition, two weight-based doses of cefazolin will be administered within 24 hours postoperatively.

< 120 kg – patients will receive 2 grams of cefazolin
≥ 120 kg – patient will receive 3 grams of cefazolin

Patients with documented allergy/anaphylactic reaction to penicillin or cephalosporin may receive intravenous vancomycin (15mg/kg or <80 kg = 1 gram, 80-99 kg = 1.25 grams, 100-120 kg = 1.5 grams, >120kg = 2 grams) monotherapy or dual therapy with vancomycin (15mg/kg or <80 kg = 1 gram, 80-99 kg = 1.25 grams, 100-120 kg = 1.5 grams, >120 kg = 2 grams) and gentamicin 1.5-5 mg/kg as an alternative. If allergic, patients will also receive two weight-based doses vancomycin postoperatively but not gentamicin postoperatively. In addition, the use of clindamycin as an alternative is also permitted at a minimum recommended dose of 600 mg or 900 mg.

Vancomycin schedule: one dose preoperatively, one dose 8-12 h postoperatively, one dose 24 h postoperatively (optional).

The application of **topical antibiotics (sprinkled into the wound)** such as vancomycin powder or antibiotic beads prior to wound closure in addition to standard parental peri-operative antibiotics is a protocol violation and is **not** permitted.

- Intra-operative re-dosing may be required to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the drug or if there is excessive blood loss (>1500 mL) during the procedure. Re-dosing of antimicrobials is recommended to occur at intervals of 1-2 times the half-life of the drug. The re-dosing intervals should be measured from the time of administration of the preoperative dose and should occur at the following intervals:

Antibiotic	Normal Renal Function	Renal Insufficiency (<30ml/min)
Cefazolin	4 hours	4 hours
Clidamycin	6 hours	6 hours
Gentamicin	No re-dosing	No re-dosing
Vancomycin	12 hours	24 hours

There should be no need to intra-operatively re-dose gentamicin or vancomycin.

3.3.2. RANDOMIZATION

After informed consent is obtained and the screening interview is conducted, the principle investigator/sub-investigator or research assistant will electronically randomize a patient to a study group intervention within 45 business days before the patient's surgery date using the REDCap database (web-based secure database application maintained by the Duke Investigators). Patient will be informed of the results of the randomization prior to surgery (call, face-to-face, secure message in HER). The Duke Statistical Investigator (Department of Biostatistics and Bioinformatics, DUMC, Durham, NC) will provide the randomization scheme that will be used within the REDCap database to randomly assign patients to one of the two treatment groups. A block randomization scheme stratified by site will be used in order to preserve treatment group balance within site. The block size will be undisclosed. Each patient who qualifies for entry into the study will be assigned a unique study number in chronological order within the participating site (i.e., site ID + patient ID).

4. STUDY POPULATION

The study population will include patients undergoing elective total knee arthroplasty by surgeons from the participating sites. All patients who present for evaluation for primary total knee arthroplasty will be screened to determine their study eligibility. Only patients who meet inclusion criteria based on the study screening protocol will be eligible for study participation. Approximately 40 sites will be invited to participate in this study and enrollment will be competitive due to the size of some sites.

4.1. INCLUSION CRITERIA

1. Patient is ≥ 18 years of age
2. Patient has no open wounds on operative leg
3. Patient is scheduled to undergo elective total knee arthroplasty for posttraumatic, osteoarthritis, avascular necrosis, and/or inflammatory arthritis
4. Patient does not have active infection on the operative leg, the operative joint
5. Patient is willing to cooperate and follow study protocol and visit schedule

4.2. EXCLUSION CRITERIA

1. Patient is ≤ 18 years of age
2. Patient is pregnant
3. Patient is unable to provide written consent
4. Patient has psychiatric disorder that precludes safe study participation or that necessitates confinement in a custodial environment at home or in a chronic care facility
5. Patient has traumatic injury that requires emergent or urgent total knee arthroplasty (e.g. fracture)
6. Patient has active infections in the operative leg/joint
7. Patient has severe dementia
8. Suspicion of illicit drug abuse by patient. Patients who use prescription cannabinoids are not excluded from enrollment.
9. ASA score of 5 & 6
10. No application of topical antibiotic powder such as vancomycin or antibiotic beads in surgical wound
11. Intra-operative re-dosing other than specified re-dosing intervals or without excessive blood loss (<1500mL)
12. History of prior native septic knee arthritis

4.3. ECONOMIC ANALYSIS (at primary (Duke University) coordinating site only)

The costs of antibiotics, treatment of postoperative complications including the cost of re-intervention, and the cost of hospital stay will be assessed at the primary coordinating site. Cost-comparison and cost effectiveness analyses will be based on the economic perspective (facility specific costs, reimbursement) of Duke University Hospital, a 919-bed Level-I university hospital. Effectiveness will be defined as the percentage of infection-free patients. These costs will be added, summed over all patients, and divided by group size. The direct medical costs of treating postoperative complications during the hospital stay will be included in the analysis. Indirect costs (loss of productivity by the patient) will not be taken into account for this analysis.

To assess the cost per complication, two distinct data sets will be analyzed: resource use, i.e., the type and frequency of goods and services (consults, additional imaging, number of physical therapy services) rendered to the patients on the one side, and the monetary values (prices and unit costs) for each type of these variables on the other side. The following goods and services rendered to the patients specifically for diagnosis and treatment of postoperative complications will be obtained from the medical records of each clinical study patient who develops a postoperative complication:

(1) operative interventions and anesthetic procedures
(2) other complication-related physicians' consultations and services
(3) artificial respiration, nutritional support, and dialysis
(4) radiography and ultrasonography
(5) physical therapy
(6) antibiotics and other complication-related medications

Prolonged hospital length of stay and days in the intensive care unit will not be included because these resources cannot be unambiguously attributed to postoperative complications. Diagnostic and therapeutic services will be valued according to the current Medicare reimbursement rate. Pharmaceuticals, devices, and material costs will be valued at hospital purchasing prices.
In a cost comparison analysis, the per-patient costs and treating complications will be added for the study, and patients in all treatment groups will be compared with one another. Cost-effectiveness analysis will be performed by dividing the per-patient costs of antibiotic drug and treating postoperative complications with the percentage of complication-free patients.

5. STUDY PROCEDURES/DATA COLLECTION

5.1. SCREENING STUDY PROCEDURES

Patient demographics and screening

Once a patient is deemed a surgical candidate for elective total knee arthroplasty, age, gender, and anthropometric assessment will be recorded in the electronic data management system. This is an essential part of the screening process and includes documentation of body weight, height, BMI, age, gender, and race. In addition, the patient's allergy status with respect to antibiotics will be documented.

Clinical Data Collection/Submission

Study data will be collected on specific REDCap forms that can be printed directly from the database.

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) assesses an individual's comorbidity level by documenting both the number and severity of pre-defined comorbid conditions.[43, 44] It provides a weighted score of a patient's comorbidities which can be used to predict short- and long-term outcomes such as function, hospital length of stay, and mortality rates. The CCI is one of the most widely used scoring systems for comorbidities (see table). This information will be collected at the baseline screening.

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

5.2 PERIOPERATIVE STUDY PROCEDURES/DATA COLLECTION

The following data points will be collected during the index procedure and recorded in the electronical data management system.

1. Use of tourniquet including tourniquet time
2. Surgical approach (e.g. medial parapatellar, midvastus, subvastus, lateral)
3. Use of tranexamic acid/aminocaproic acid/desmopressin and route of administration (intravenous, oral, topical)
4. Use of closed suction versus reinfusion drain versus no drain
5. Type of wound closure (e.g running subcuticular, nylon, staples)
6. Type of wound dressing used (incisional negative pressure dressing, hydrofiber silver-impregnated dressing, occlusive/island wound dressing, cotton-based absorbent dressings, etc).
7. Type of antibiotic given (time and route), antibiotic redosed? (yes/no, time)
8. Time of surgical incision
9. Laterality
10. Type of anesthesia (e.g general, regional, and/or local infiltration)
11. Use of antibiotic cement (yes/no, type)
12. ASA score

American Society of Anesthesiologists (ASA) physical status score

The ASA physical status classification system is a system for assessing the fitness of patients before surgery.[45] In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system; a sixth category was later added. These are:

1. Healthy person.
2. Mild systemic disease.
3. Severe systemic disease.
4. Severe systemic disease that is a constant threat to life.
5. A moribund person who is not expected to survive without the operation.
6. A declared brain-dead person whose organs are being removed for donor purposes.

5.3.1 FOLLOW-UP EVALUATION (90-day)

Surgical Site infection/Periprosthetic Infection Status

The primary outcome measure will be the rate of periprosthetic infection (PJI) after elective total knee arthroplasty. For each enrolled and randomized subject, the 90-day PJI rate and causing organism if PJI occurred will be reported. The definition of periprosthetic infection exists when the following criteria are met[46]:

1. There is a sinus tract communicating with the prosthesis; or
2. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or
3. Three out of the following five criteria exist:

    - Elevated serum erythrocyte sedimentation rate (ESR) >30mm/Hr in chronic setting AND serum C-reactive protein (CRP) >100mg/L in acute setting or 10,g/L in chronic setting concentration,
    - Elevated synovial leukocyte count OR ++change on leukocyte esterase, positive synovasure test
    - Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) >10,000 cells/uL in acute setting and > 3,000 cells u/L in chronic setting
    - Isolation of a microorganism in single culture of periprosthetic tissue or fluid, or
    - Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification.

5.3.2 12-MONTH FOLLOW-UP EVALUATION

Periprosthetic Infection Status

The one year rate of periprosthetic infection (PJI) after elective total knee arthroplasty will be recorded. Sites are encouraged to assess 12-months PJI rate (office visit, phone call, secure messaging such as MyChart or text message via REDCap) and causing organism if PJI occurred. However, this is can be done automatically utilizing an email survey function in the REDCap database if patients consent to this process and provide a phone number and/or email address. This will greatly reduce the burden on participating sites. The definition of periprosthetic infection exists when the following criteria are met[46]:

4. There is a sinus tract communicating with the prosthesis; or
5. A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or
6. Three out of the following five criteria exist:

   - Elevated serum erythrocyte sedimentation rate (ESR) >30mm/Hr in chronic setting AND serum C-reactive protein (CRP) >100mg/L in acute setting or 10mg/L in chronic setting concentration,
   - Elevated synovial leukocyte count OR ++change on leukocyte esterase, positive synovasure test
   - Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) >10,000 cells/uL in acute setting and >3,000 cells u/L in chronic setting
   - Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or
   - Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification.

5.4. SCHEDULE OF ACTIVITIES

Activity	Screening/Enrollment	Index Procedure	90-day follow-up	12-months follow-up
Inclusion/Exclusion criteria	**X**			
Age	**X**	**X**		
Gender	**X**			
BMI (weight, height)	**X**			
Race	**X**			
ASA		**X**		
CCI	**X**			
Laterality	**X**	**X**		
Surgical approach		**X**		
Tourniquet use/time		**X**		
Drain use/type		**X**		
TXA/amicar use		**X**		
Type of skin closure		**X**		
Use of abx cement		**X**		
Randomization, ABX	**X**			
Type of abx used and re-dose intraop status		**X**		
Type of anesthesia		**X**		
SSI/PJI events			**X**	**X**
PJI causing organism			**X**	**X**

Patient allergy status	**X**			
Study completion status			**X**	

Grey fields represent extended dataset and data collection is not mandatory.

6. STUDY DURATION

This study is designed as a prospective longitudinal study with participants remaining in the study for 90 days after TKA surgery. Data collection for each individual study participant will be concluded at the 90-day post-surgical follow-up visit. In addition, there is a 1-year follow-up assessment of the periprosthetic joint infection rate (PJI).

7. DATA MANAGEMENT

Data will be collected and managed using REDCap. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture. REDCap was developed by Vanderbilt's CTSA and is currently used and supported by thousands of consortium partner institutions. REDCap at Duke is managed and supported by the Duke Office of Clinical Research (DOCR) Research Management Team, located in the School of Medicine. RMT provides research and data management support to investigators and collaborators. Standard operating procedures will be developed to ensure data quality. Monthly performance reports will summarize: patients recruited, patients successfully randomized, and the extent of follow-up for the enrolled patients. The reports also will evaluate the completeness of collected study data, 90-day, and 12-months periprosthetic joint infection rate if available.

Each site will be responsible for data entry and the following steps should be followed while completing the CRFs:

1. Complete data carefully and accurately
2. Complete header information consistently across all case report forms for each individual study subject
3. Ensure that all fields are completed

Data Submission

Completed CRFs will be submitted directly to the Coordinating Center by REDCap, every effort must be made to ensure data submission to coordinating center is made within 90 days of the visit completion. The use of disclosure of all protected health information will comply with the Health Insurance Portability and Accountability Act (HIPAA).

Reporting Requirements

Investigator Reporting Responsibilities

The investigator will be responsible for the accuracy, completeness, and timeliness of data reported to the Coordinating Center in accordance with this protocol. The Investigator or Designee will ensure timely reporting to their IRB/IEC as required by their local institution to maintain the approval throughout the study, and will provide any required final reporting upon study completion/termination. A copy of all IRB or EC re-approval letters must be submitted to the Coordinating Center. The coordinating center will provide monthly reports to participating sites.

REDCap Features

- HIPAA-compliant and secure. Data are stored on a Duke server behind firewall.
- Intuitive, web-based interface for database build, data entry, and reporting
- Data validation, audit trail, branching logic, and calculated fields
- Data dictionary for easy project edits and duplication
- Automated data export (.csv, SPSS, SAS, Stata, R)
- Data import from external sources
- Ability to add users external to Duke

8. STATISTICAL ANALYSIS

Data will be summarized and presented using the mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum for continuous variables and counts with percentages for non-missing categorical variables unless otherwise stated. All analyses will be performed as intention-to-treat with sensitivity analyses for subjects lost to follow-up. The primary endpoint (90-day infection rate) will be compared between treatment groups using the chi-square or Fisher's exact test (expected cell counts < 5) using subjects who have an infection or complete follow-up through Day 90. A Kaplan-Meier analysis will be used as a sensitivity analysis to include subjects lost to follow-up. Comparisons between continuous variables at baseline will use either a t-test or Wilcoxon rank sum test, dependent on the variable distribution. Univariable and multivariable logistic and/or Cox proportional hazards regression models will be used to adjust for the effects of possible baseline confounders (ASA, CCI, age, tourniquet use and time, drain use, TXA/amicar/desmopressin, wound dressing, skin closure modality) on the occurrence of infection. All analyses will be performed using SAS version 9.4 or higher (SAS Institute Inc., Cary, North Carolina) by the Duke Statistical Investigator. A p-value < 0.05 will be considered statistically significant unless otherwise specified. Patients who received the wrong number of doses will result in a reportable deviation and captured in REDCap. This data will be analyzed separately at the end of the study. If the number of patients that received the wrong number of doses impacts the calculated power, additional study subjects will be enrolled.

9. PRIVACY AND CONFIDENTIALITY

Participant Confidentiality

- Any information that could identify study participants (i.e. names or medical record numbers) will not be included on study data forms. Instead each study participant will be given a study number. Only the study staff will be able to link the study numbers to the names of study participants.
- Data forms will be stored in a cabinet in a locked office.
- Data collected during the study will be stored electronically in cloud based electronic data management system that is password protected. Only personnel on the study team will have access to this data.
- The names, medical record numbers, or any other unique identifiers of study participants will not be included in any publications resulting from this study. To protect data stored on computers, passwords will be used and will be changed regularly.
- Backup copies of all data stored on the computer will be made at specified time intervals
- Research records will be stored in a research study file separate from the study participants' medical records.

9.1. INFORMED CONSENT

Written informed consent will be obtained from all subjects before any study related procedures are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject under consideration for enrollment is given a full explanation of the study. This process must be documented on a written Informed Consent Form (ICF) that has already been reviewed and approved by the same Institutional Review Board and/or Independent Ethics Committee (IRB/IEC) responsible for approval of the protocol. Each ICF shall include the elements required by Food and Drug Administration (FDA) regulations in 21 (CFR) Part 50 and International Committee on Harmonization (ICH) Good Clinical Practice (GCP).

Once the investigator or designated research personnel have fully explained the study and answered all the potential questions the participant may have and it is agreed that the participant understands the implications of participating, the IRB approved informed consent form should be signed and dated by all applicable parties in accordance to the IRB/IEC requirements. Study team should give a copy of the signed consent form to the participant and the original should be kept in study subject binder or regulatory binder. Explanation of study and the signing of the informed consent must occur prior to the subject's participation in the trial.

If the patient meets the study entry criteria, the study will be introduced to them by study personnel staffing the total joint clinics. A thorough explanation of the study will be provided to the patient and adequate time will be provided for the potential participant to thoroughly read the consent form and to ask and have all questions about study

participation answered. The prospective participants will be encouraged to discuss the study and their potential participation in the study with their family members or significant others. The patient must be able to read the consent form in order to participate in the study. The patient will either provide a written signature to signify their agreement to participate in the study or they will decline study participation. In cases in which the patient decides not to participate in the study, they will be provided with the standard of care at the institution for their surgical procedure.

During the informed consent process, potential study participants will be informed that they may discontinue study participation at any time. If a study participant chooses to withdraw from the study, they will be asked to notify the principal investigator or a member of the study staff of their intentions.

During the informed consent process, potential study participants will be informed that the electronic data capture system, REDCap can perform automated follow-up via email and text messages. The potential study participants are asked to provide valid email address and/orcell phone number. Alternatively, participants may be contacted via secure messaging portal (i.e. MyChart) to obtain follow-up data.

Potential study participants also will be told that the principal investigator may choose to withdraw a study participant from the study for reasons related to noncompliance with the study protocol or if an event occurs that would warrant this decision. In such cases, the principal investigator will provide an explanation for the decision and the reason why the decision was made. Specific data forms will be completed to document the reasons for study participant withdrawal from the study. In addition, the principal investigator at each site may withdraw study participants from the study after consent and randomization but before administration of the antibiotic for medical concerns. This needs to be indicated in the electronic data capture system as withdrawn at principal investigator discretion.

9.2 RISK AND BENEFITS

Patients in either group will not be at any additional risk as a result of participation in the current study as this treatment is consistent with general current practices.

10. ADVERSE EVENTS/REACTIONS

Adverse event means any untoward medical occurrence associated with the use of the antibiotic drug in humans, whether or not considered antibiotic related.

Adverse reaction means any adverse event caused by any antibiotic drug used in the study.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the antibiotic drug used caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than “adverse reaction”

Reasonable possibility. For the purpose of safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the antibiotic drug used and the adverse event.

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator (i.e., the study site principal investigator), its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Serious, suspected adverse reaction. A suspected adverse reaction is considered “serious” if, in the view of the Investigator (i.e., the study site principal investigator), it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Unexpected, suspected adverse reaction. A suspected adverse reaction is considered "unexpected" if it is not listed in the general investigational plan, clinical protocol, or elsewhere; or is not listed at the specificity or severity that has been previously observed and/or specified.

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

  Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study.
- The test finding is considered an adverse event by the Investigator.

Unexpected, suspected rise of infection rates/study suspension. An unexpected rise in postoperative infection rate greater than 3% in total per enrolling site or among all enrolling sites will warrant a review of site specific and overall data. The finding may lead to a change in study drug dosing or discontinuation of administration and/or suspension of the study.

The following adverse events (AE) specific to the administration of antibiotics will be recorded and reported:

Criteria Used for Antibiotic-Associated Adverse Drug Events modified from Tamma et al JAMA Intern Med. 2017;177(9):1308-1315

Adverse Drug Event	Definition
Within 30 d of Antibiotic Initiation	
Non–Clostridium difficile–associated diarrhea	>3 Loose stools per day associated with antibiotic administration and documented as "diarrhea" in the medical record, in the absence of laxative use or preexisting enteritis. Patients with a positive C difficile PCR test result were excluded from this category
C difficile infection	Clinical signs and symptoms consistent with C difficile infection in the setting of a positive C difficile PCR test resultand the absence of laxative use
Nausea and vomiting	Nausea and vomiting associated with antibiotic administration, in the absence of an alternate explanation
Hematologic	Anemia (hemoglobin level <8 g/dL), leukopenia (white blood cell count <4500 cells/μL), or thrombocytopenia (platelet count $<150 \times 10^3/\mu L$) with levels below patient's baseline and in the absence of significant intraoperative bleeding and documented blood loss or myelosuppressive therapies

Hepatobiliary	Cholestasis (total bilirubin level >3 mg/dL) or transaminitis (aspartate transaminase or alanine transaminase level >3 times patient's baseline) in the absence of existing hepatobiliary disease or recent biliary instrumentation
Renal	Increase in serum creatinine level >1.5 times patient's baseline in the absence of precipitating factors for acute kidney injury such as sepsis or the receipt of intravenous contrast or other nephrotoxic agents
Neurologic	Altered mental status, peripheral neuropathy, or seizures in the absence of preexisting neurologic conditions, substance-related toxic effects, opioid related mental status change, or infectious syndromes
Dermatologic	Rash, including hives, non-hives rashes, and red man syndrome, temporally associated with antibiotic administration with resolution on antibiotic discontinuation; excluding vancomycin-associated red man syndrome
Cardiac	QTc >440 ms in males or >460 ms in females in the absence of preexisting arrhythmias, based on ≥2 electrocardiograms
Anaphylaxis	Acute onset of respiratory compromise, hypotension, or end-organ dysfunction within minutes after initiation of antibiotic administration, in the absence of an alternative explanation
Myositis	Increase in creatine phosphokinase level >5 times patient's baseline, in the absence of existing myopathy or statin use

Abbreviations: PCR, polymerase chain reaction.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10.0; to convert white blood cell count to ×109 per liter, multiply by 0.001; to convert platelet count to ×109 per liter, multiply by 1.0; to convert bilirubin to micromoles per liter, multiply by 17.104.

All reported adverse events will be reviewed by the PI on a monthly basis and escalated as needed.

11. DATA SAFETY MONITORING

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the antibiotic administration will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained in order to permit: 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event* and; 2) an assessment of the casual relationship between the adverse event and the antibiotic administration.

Adverse events or abnormal test findings felt to be associated with the antibiotic administration /drug will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Investigator. The Principle Investigator will review adverse events monthly using an automated REDCap report and prepare a case summary for quarterly review by the DATA Safety Committee consisting of Duke Faculty members. The DATA Safety Committee will review cases with adverse events and monitor overall infection rate on a quarterly

basis. A written report of each meeting will be placed in REDCap and distributed to participating sites. These reports will also support the annual continuing review.

Members of the Data Safety Committee are:

1. Thorsten M. Seyler, MD PhD (PI, Duke University, Orthopaedic Surgery)
2. William A. Jiranek, MD (Duke University, Orthopaedic Surgery)
3. Edward Hendershot, MD (Duke University, Infectious Disease)
4. Jessica Seidelman, MD (Duke University, Infectious Disease)

In accordance with applicable policies of the Duke University Institutional Review Board (IRB) which will also serve as the primary IRB for the study, the Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the antibiotic administration;* 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible following the investigator's receipt of the respective information. Adverse events which are 1) *associated with the antibiotic administration*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting, the Investigator will report the adverse event to the IRB as soon as possible after the determination was made.

12. ETHICS/CONFLICT OF INTEREST

The clinical research study will be conducted in accordance with the current IRB-approved clinical protocol; International Conference of Harmonization (ICH) Good Clinical Practice (GCP) Guidelines adopted by the FDA; and relevant policies, requirements, and regulations of the Duke University IRB, State of North Carolina, and applicable federal agencies.

None of the principal investigators, co-investigators or study team members should perform, for any personal gain, services to any supplier of goods or services, as employee, consultant, or in any other capacity which promises compensation of any kind, unless the fact of such transaction or contracts are disclosed in good faith, and the board or committee authorizes such a transaction. Similar association by a family member of principal investigators, co-investigators or study team members or by any other close relative may be inappropriate.

Currently, there are no consultative relationships that the principal or co-investigators have with any entity related to the protocol that might be considered a conflict of interest.

13. PUBLICATION & PRESENTATION PLAN

The dissemination of clinical data will include the timely presentation of results at the following scientific congresses and orthopaedic society meetings:

- American Association of Hip and Knee Surgeons (AAHKS) Annual Meeting, Dallas, Texas
- American Academy of Orthopaedic Surgeons (AAOS) Annual Meeting

In addition, the primary investigators and co-investigators will submit a full-length manuscripts summarizing the results of the study to the following peer reviewed medical and specialty journal. Sub-analyses of other variables and the impact on the primary outcome measures will be published as deemed scientifically appropriate.

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