Major Extremity Trauma Research Consortium (METRC):

Local Antibiotic Therapy to Reduce Infection after Operative Treatment of Fractures at High Risk of Infection: A Multicenter Randomized, Controlled Trial
[FDA IND #119891]
NCT02227446

Sponsored by: DOD CDMRP

Contract Number: W81XWH-10-2-0134

Principal Investigator/Protocol Chair: Robert V. O'Toole, MD

Medical Monitor: Marc Swiontkowski, MD

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This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from METRC (or others, as applicable), unless it is necessary to obtain informed consent from potential study participants.

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Signature Page

The signature below constitutes the approval of this protocol and the attached appendices, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

The Lead Principal Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal Investigator: _____

Print/Type

Signed: _____ Date: _____

Name/Title

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List of General Abbreviations/Terminology

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA ©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NDA	New Drug Application
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

List of METRC Abbreviations/Terminology

AFIRM	The Armed Forces institute of Regenerative Medicine
CDMRP	Congressionally Directed Medical Research Program.
CCCS	Civilian Core Clinical Sites
DOD	Department of Defense
DOD HRPO	DOD Human Research Subject Protection Office.
DOD PRORP	Department of Defense Peer Reviewed Orthopaedic Research Program
Master Consent Form	Template consent form designed for study by the MCC
Master IRB application	Template IRB application designed for study by the MCC
MCC	METRC Coordinating Center of the Consortium
MCC Study Manager	Principal site contact for Research Coordinators at sites
MTF Core Clinical Sites	Military Treatment Facilities Core Clinical
OETRP	Orthopaedic Extremity Trauma Research Program
PPM	Policy and Procedure Memorandum
SCC	Satellite Clinical Sites
AI	Site Associate Investigators.
RC	Site Research Coordinator
RS	Site Research Staff
Study Number	Protocol identification number
Study Principal Investigator	Lead Investigator on a protocol
Study Protocol Committee	Protocol development
REDCap	Research Electronic Data Capture System
USAMRMC	United States Army Medical Research and Material Command

PROTOCOL SUMMARY

Title: Local Antibiotic Therapy to Reduce Infection after Operative Treatment of Fractures at High Risk of Infection: A Multicenter Randomized, Controlled Trial

Sponsor: DOD PRORP

Type of study: Prospective Randomized Controlled Trial

Primary Aim: Compare the proportion of deep surgical site infections within 6 months in patients treated with local Vancomycin powder compared to those treated without local Vancomycin powder.

Primary Hypothesis: The proportion of deep surgical site infections will be lower for patients treated with local Vancomycin powder.

Secondary Aim #1: Compare antibiotic sensitivities of the bacteria in the patients who develop deep surgical site infections in study patients treated with local Vancomycin powder compared to those treated without local Vancomycin powder.

Hypothesis 1: In the patients who develop infections, the antibiotic sensitivity profiles between patients treated with local Vancomycin powder will be non-inferior to those treated without local Vancomycin powder.

Secondary Aim #2: Build and validate a risk prediction model for the development of deep surgical site infections in patients treated without local Vancomycin powder. (b) Explore whether the effect of local Vancomycin powder is modified by the predicted risk of infection.

Hypothesis 2: Patient (e.g. medical co-morbidities) and injury (e.g open fractures) factors will be highly predictive of infection risk.

Hypothesis 3: Patients with higher predictive risk will experience greater benefit from local antibiotics.

Study design: The proposed study is a multi-center, prospective randomized controlled trial comparing treatment with and without the local Vancomycin powder at the time of fracture fixation.

Study duration: 24 months; 12 month enrollment period, 6 month patient follow up.

Sample size: 500 patients will be consented per arm.

Number of study sites: Over 15 sites will be included which is made up of a Combination of subset of 24 Core METRC and 4 MTFs not able to enroll in competing METRC studies, and 30+ METRC satellite sites.

Inclusion criteria

1. All "high energy" tibial plateau fractures treated operatively with plate and screw fixation. We define "high energy" tibial plateau fractures as patients who are either:
   1.1 Initially treated with an external fixation (with or without limited internal fixation) and treated definitively more than 3 days later after swelling has resolved.
   1.2 Any open type I, II, or IIIA fracture, regardless of timing of definitive treatment.
   1.3 Any tibial plateau fracture associated with ipsilateral leg compartment syndrome fasciotomy wounds.

2. All "high energy" pilon (distal tibial plafond) fractures treated operatively with plate and screw fixation. We define "high energy" pilon fractures as patients who are either:
   2.1 Initially treated with an external fixation (with or without fibula fixation or limited internal fixation) and treated definitively more than 3 days later after swelling has resolved.
   2.2 Any open type I, II, or IIIA fracture, regardless of timing of definitive treatment.
   2.3 Any tibial pilon fracture associated with ipsilateral leg compartment syndrome fasciotomy wounds.

3. Ages 18 to 80 years
4. Patients may have co-existing non-tibial infection, with or without antibiotic treatment.
5. Patients may have risk factors for infection including diabetes, immunosuppression from steroids or other medications, HIV, or other infections.
6. Patients may have a head injury
7. Patients may have a portion of the fixation (e.g. fibula fixation in pilon or percutaneous screws across a tibial plateau fracture) prior to definitive plate fixation, at the initial surgery before randomization.
8. Patients may have other orthopedic and non-orthopaedic injuries.
9. Patients may have pre-existing musculoskeletal injuries, be non ambulators, or have spinal cord injuries.
10. Women and minorities are included.

Exclusion criteria

1. The study injury: tibial plateau, pilon, is already infected at time of study enrollment.
2. Patient speaks neither English nor Spanish.
3. Patients who have already had definitive fixation prior to enrollment in the study.

4. Severe problems with maintaining follow-up (e.g. patients who are homeless at the time of injury or those how are intellectually challenged without adequate family support).
5. Patients with allergies, drug administration reactions, or other sensitivities to Vancomycin (such as a history of Redman's Syndrome).
6. Pregnancy.
7. The study injury is a type IIIB or IIIC open fracture.

Outcome measures

Primary Outcome Measure: Surgical Site Infection. The main outcome measure will be the presence of clinically significant deep SSI in the first 24 weeks after surgery, as determined by CDC guidelines for determining surgical site infection [24,34,51]. These guidelines were developed to provide clear, objective criteria for evaluating surgical wounds and determining the presence or absence of infection. The CDC criteria is currently 3 months for surgical site infection and our pilot data indicate that 85% of the infections in this population happened in the first 3 months [72]. To help capture more infections, we have moved the timeframe back to 6 months.

Wound characteristics will also be evaluated using the ASEPSIS score [15,16,84,85]. In this system wounds are scored using the weighted sum of points assigned for predetermined criteria including the need for Additional treatment, presence of Serous drainage, Erythema, Purulent exudates, Separation of deep tissues, the Isolation of bacteria, and the duration of patients Stay (ASEPSIS). This system of wound scoring complements the CDC guidelines by providing a means to grade the severity of infection as does the METRC standardized infection CRF which records culture data, laboratory values (as obtained as part of standard clinical care by site), and other parameters to help insure validity of the primary outcome measure.

In keeping with the CDC definition, we will define deep infections as those that require operative treatment, and superficial infections as those that are treated without operative intervention. Based on our previous oxygen study using the same patient population, we expect that 85% of infections in this patient population to require operative treatment and to have an overall deep infection rate around 11.5% [72].

Secondary Outcome Measure: Bacterial Sensitivities: Secondary outcome measures in this study include culture data in the group that becomes infected. All deep surgical site infections will have sterile intraoperative wound cultures taken, as is currently performed in routine clinical practice. Sensitivities of the isolated bacteria, which are also determined routinely in current clinical practice, will be recorded for analysis. Theoretically, the use of the local Vancomycin powder might influence the sensitivity of bacteria to certain antibiotics in the patients who become infected.

It might be anticipated that bacteria in patients with infections that develop in the treatment group might be less susceptible to Vancomycin as this is the antibiotic used in this technique. The most common bacterial isolates in infection after orthopaedic fracture care are methicillin resistant *staph. aureus and methicillin resistant coagulase negative Staphylococci*. These bacteria are frequently susceptible to Vancomycin, and the occurrence of Vancomycin resistant (meaning the drug is not effective against the bacteria) strains of staph aureus and coagulase negative staphylococci would be clinically concerning. We do not anticipate this occurring but will use the rate of Vancomycin sensitivity as an outcome measure in the patients with staph. infections as a secondary outcome measure. The appearance of additional clinically relevant bacterial susceptibilities will also be monitored as part of the study.

Risk Factors for Infection: All demographic characteristics of the patient, the descriptors of the injury, and details of the surgical treatment that would be available prior to the implant of the local Vancomycin powder will be collected for analysis regarding determination of a model to predict infection risk in this patient population. This analysis will aid clinicians in determining risk for postoperative infection as well as help determine which patients are most likely to benefit from the local Vancomycin powder technique.

Demographic variables will include age, presence of co-morbidities such as diabetes, smoking history, history of prior musculoskeletal infection, and history of infection within the past 30 days.

Injury descriptors will include injury mechanism, open or closed fracture type, AO classification of the fracture type, other orthopaedic injuries, and other non-orthopaedic injuries.

Treatment parameters will include time from injury to definitive treatment, time from injury to external fixation (for the tibial plateau and pilon fractures), and surgical approaches used (for the tibial plateau and pilon fracture).

Protocol Committee- Responsible for developing a detailed study protocol, provides oversight on study progress and acts to correct deficiencies in the conduct of the study. This committee also drafts the main publications related to the study.

Steering Committee- Steering Committee is the decision making body of the Consortium and makes decisions regarding study design issues, study procedures, allocation of study resources and priorities for meeting competing demands of the Consortium and individual studies. The Steering Committee is composed of Site Investigators from each core METRC clinical center, the Department of Defense Program Officer for METRC, the orthopaedic consultants from the Army, Navy and Air Force, regional representatives of Satellite Clinical Centers, and the Director, Deputy Director, Principal Biostatistician and Principal Economist of the Coordinating Center. The Steering Committee is responsible for approving the protocol.

METRC Coordinating Center- Responsible for maintaining all study documentation, developing and maintaining the master IRB application and consent, circulating any changes to study documents including protocols, case report forms, and IRB materials to each participating center, providing daily oversight and management of study implementation, providing payment to sites for patients enrolled, performing site monitoring, data quality control and analysis of study results.

Core and Satellite Clinical Sites- Responsible for the conduct of clinical studies including patient enrollment, performing study procedures, data collection and conducting study follow-up visits.

Publication Committee- Responsible for reviewing manuscripts prior to journal submission and reviewing presentations prior to presentation; for mediating and settling disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations; for preparing and maintaining a list of concepts for publications and preparing and maintaining a list of approved METRC publications, which shows the status of each manuscript from initiation through publication.

DSMB- Independent Data and Safety Monitoring Board (DSMB) appointed by DOD, responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality.

Medical Monitor- Responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of safety reports; resolving safety issues; and interacting with Principal Investigators.

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

The treatment of high-energy military fractures continues to have poor outcomes and is associated with high rates of infection. The use of local antibiotics associated with fracture hardware has potential to reduce complications by lowering infection rates in these patients. Our hypothesis is that the use of sterile local Vancomycin powder for fractures at high risk for infection will reduce infection rates and therefore improve outcomes compared to treatment without the local antibiotics. The results of this trial have potential to reduce surgical site infection within both the military and civilian sectors and therefore improve patient outcomes from these potentially devastating injuries.

1.2 Problem Definition: Infection after Fracture Fixation

Infection continues to be a common complication associated with treatment of high-energy military fractures [20,22,33,38,43,59,62]. As with high-energy civilian fractures, a high rate of hospital re-admission for complication have been observed, and these complications have been linked to poor medium and long-term outcomes[11,31]. Hospital re-admission for complications such as infection was one of the most important predictors of poor outcome in the Lower Extremity Assessment Project (LEAP) study, a prospective multi-center study on high- energy trauma [11]. The LEAP study reported that the re-hospitalization rate for complications after severe open fractures is as high as 57% and one of the major drivers of hospital re- admission is deep infection [11,31].

Traditional treatment protocols for high energy lower extremity fractures have demonstrated rates of surgical site infection and osteomyelitis ranging from 14.3%% - 60.0% [11,20,22,31,33,38,43,59,62,74] in both military and high energy civilian settings. Traditional treatment protocols typically utilize metallic hardware (plates and screws or nails) for fracture fixation, which have the disadvantage of placing metal within the fracture site. Multiple studies demonstrate that infection rates tend to increase whenever hardware is placed within a wound [67,68,71], likely due to the difficulty the immune system has in clearing bacteria from the biofilm that develops on metallic surfaces [28,67]. High- energy military injuries have a particularly high risk of infection [20,22,33,38,43,59,62].

Surgical site infection is a major treatment challenge in the military, but it continues to cause significant morbidity in civilian applications as well. Surgical site infection in general is the most common potentially preventable post-operative complication with estimates of $1.8 billion spent in treatment of surgical site infection each year in the United States [13,14,71]. Any treatment strategy that could reduce surgical site infection would certainly make an important contribution to the care of our wounded soldiers, but also the care of orthopaedic trauma patients in general.

Intravenous (IV) antibiotics are routinely given at the time of all fracture fixation surgery to decrease the rate of surgical site infection [13,14, 63,90]. The efficacy of prophylactic IV antibiotics

and the importance the timing of the delivery of these antibiotics have been well studied and shown to be efficacious [13,14, 63, 90]. The use of these systemic antibiotics is currently the standard of care.

Despite the success in using IV antibiotics as a prophylaxis against wound infection, in some ways systemic antibiotics are an inefficient strategy to prevent infection associated with the surgical treatment of fractures. The mechanism of the beneficial effect of systemic antibiotics is thought to be in delivery of antibiotics to the site of the surgery; however antibiotics are delivered throughout the body where it is not needed. This limits the amount (dose) of antibiotics that can be delivered at the surgical site else risk toxicity to other remote organ systems.

Intravenous antibiotics also are only delivered to tissues that have a blood supply since the antibiotics are administered into the systemic circulation. Tissues that are traumatized frequently have a compromised blood supply. Further, all foreign material such as the metallic plates used in fracture fixation, have no blood supply so antibiotics are not delivered to the plate surface where bacteria commonly adhere and colonize the surgical site.

Local antibiotics hold promise to reduce surgical site infection in general [91,92,96] and in particular in high energy fracture patients such as those seen in military injuries. The mechanism of infection after fracture surgery is typically that bacteria adhere to the metal plates at the time of surgery and "colonize" the plate [28,67,68]. The bacteria create a "biofilm", a protective layer that sequesters the bacteria from the body's immune system and allows the bacteria to multiply and eventually lead to surgical site infection [28,67,68]. Local antibiotics attempt to disrupt this cycle by sterilizing the wound bed and preventing the development of the biofilm [30,36,44,71].

Traditionally orthopaedic trauma surgeons who wish to use this concept of local antibiotics are forced to create their own antibiotic delivery devices. Surgeons create "antibiotic beads" out of cement (polymethy methacralate) that is impregnated with antibiotics and then placed within the wound [93,94,95]. Fracture surgeons also use this concept when they create an intramedulary nail out of antibiotic impregnated cement to help clear infections after fracture treatment [6].

Antibiotic beads are an imperfect solution as they require removal of the antibiotic beads at another surgery, and the beads themselves take up space making them impractical in many fracture types as they may make wound closure difficult or impossible. There are some dissolvable compounds that can be placed in a wound, but the existing products tend to drain fluid that looks like drainage associated with infection so they are rarely used in clinical practice for prophylaxis against infection.

Although there is great interest in the use of local antibiotics to help decrease the rate of infection, currently orthopaedic trauma surgeons rarely have a way to implement this strategy. This concept has particular appeal for military extremity injuries because these injuries are

associated with high rates of infection and significant local tissue damage making intravenous antibiotics less efficacious. A strategy for sterilizing the wound at the time of fracture surgery and preventing the colonization of the orthopaedic implants may have significant clinical benefit, but to date no such technique is widely used for these patients.

1.4 Novel Approach: Local Vancomycin Powder

Implantable medical devices incorporating antibiotics to reduce the risk of implant related infection have been used clinically in orthopedic surgery for decades [36] and continue to evolve [68]. The concept of a sleeve or pouch added to an implantable device to reduce infection has been successfully demonstrated with cardiac pacemakers [30]. These FDA-approved products have been demonstrated clinically to be safe and effective outside the realm of orthopaedics but have not yet reached the stage of clinical use in orthopaedics.

In contrast, recently several clinical studies in the spine literature have emerged describing the use of local Vancomycin powder to reduce surgical site infection [97,98,99,100,102]. These studies demonstrated that deep infections were four times as likely in patients who did not receive the local Vancomycin powder prophylaxis [97,98,99,100,101] and demonstrated a reduction in the cost of care. These studies are retrospective in nature and suffer from limitations such as selection bias, but the initial data have demonstrated remarkable reduction in infection rates in the group using the local Vancomycin powder. Additionally, these studies have demonstrated no known complications or side effects of the local use of Vancomycin [97,98,99,100]. In one study 80% of these patients had no systemic Vancomycin levels detected and 20% had very low levels that were well below clinical importance indicating the likely lack of effect of the technique on distant organs [98].

The surgical technique employed using local Vancomycin powder has been to place the sterile powder directly in the wound over the hardware and tissues at the time of wound closure [97,98,99,100]. It is thought that this creates the "kill zone" for bacteria that inhibits biofilm formation. As there is essentially no carrier for the antibiotics, the antibiotics are likely gone within a day or even less time.

It is unknown how long the antibiotics must be present in the wound to be effective, but the spine data clearly indicates that this method of delivery appears to be efficacious. It appears that there may be a critical window right around the time of surgery to reduce the rate of surgical site infection and local Vancomycin powder may play a crucial role in this period. Other methods that reduce surgical site infection such as IV antibiotics [90] are very time dependent and must be given very near the time of the surgical incision for efficacy. Further, from a concern for development of resistant bacteria it is preferable to have a high dose with broad killing over a short time period as would be present with this technique, than to have lower doses present over longer time periods which might be the case with antibiotics in longer acting carriers.

Although there is strong scientific rationale and reasonable evidence from the spine literature indicating safety and hinting at efficacy, there is no literature investigating this technique in extremity fracture surgery at risk for infection, which is of significant interest to both the military and civilian trauma populations. Anecdotally, some leading orthopaedic trauma surgeons nationally have used the technique for high-risk patients without complication and some centers (Vanderbilt for example) have used the technique for years for this application. Having said that, there is no literature to date supporting its use in patients at high risk of infection.

Vancomycin powder is appealing in technique as it is potentially applicable to every patient treated with fractures at high risk for infection in both the military and civilian domains. Additionally, there is nothing to theoretically limit such a concept from being used with any type of hardware, thus increasing the potential impact of the product on clinical practice. Surgeons could choose to use the technique in patients of high risk of infection.

There are several potential advantages of local Vancomycin powder over antibiotic coated implants. The first is ease of study design. Since Vancomycin is already clinically used, it was straightforward to obtain FDA approval for the study. Additionally, Vancomycin powder is low cost (<$10/dose) compared with the likely expense associated with these newer emerging technologies. Further, surgeons, hospitals, and operating room personnel are already familiar with Vancomycin powder so there are almost no surgeon barriers to acceptance if the technique is demonstrated to work.

Vancomycin has been chosen as the type of antibiotic for this study because of its proven track record in the spine literature [97,98,99,100] and because of its efficacy against MRSA which has emerged as the most common pathogen encountered in surgical site infection [89]. Additionally, there are no concerns regarding inhibition of bone healing or osteogenic cytotoxicity [88] or renal toxicity, especially at this relatively low dose for systemic toxicity.

2.2 Rationale

Although there is strong theoretical and promising clinical data regarding the use of local antibiotics to reduce infection, it is not yet clear that local Vancomycin powder will perform better than treatment without local Vancomycin powder in a rigorous head to head clinical trial. It is possible that the theoretical benefits of local antibiotics will not translate into reduced infections in fracture patients at risk for increased infection.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The risks associated with this study primarily concern adverse reactions to the study drugs. All drugs are FDA approved and marketed for a variety of uses. The proposed protocol is of an

investigational use of the medication Vancomycin powder that is to be placed in the orthopaedic surgical wound at the time of closure. There is no intention of the protocol to support a new indication for use or significant change in labeling of the drugs; is not intended to support a change in advertising for the drugs; will not test a new dosage of the drug, nor is it being used in a new clinical population; and the study will be conducted with informed consent and in compliance with 21 CFR 312.7 regarding promotion and sale of drugs. Patients in the study will be actively monitored for any adverse reactions. The FDA approved this study with an IND on 10/31/13 (IND #119891). The study and its investigators will comply with all FDA regulations.

All attempts will be made to minimize risk to the study volunteers; however every research study represents some risk to its volunteers including psychological, legal, social and economic risks that could be brought about by accidental release of study information into the public domain. These study risks are small, however we will have protocols in place to further minimize and monitor these risks based on SOP's developed at the coordinating center.

Additional theoretical risks inherent to this study involve the use of the local Vancomycin powder. The risk of giving antibiotic powder are increased for participants who have an allergy to the drug. In addition, there is increased risk for participants who are susceptible to local toxicity to the drug. Neither of these issues was observed in the previous clinical trials [97,98,99,100].

A sample package insert for Vancomycin power will be attached with the IRB submission. The package insert identifies risks associated with the standard use of Vancomycin powder as an IV/Injectable medication. At this time we do not know the risks associated with the current proposed delivery mechanism.

Additionally there is the risk that the technique may actually increase the risk of infection through some unknown mechanism or create some other as yet unanticipated clinically significant problem.

2.3.2 Potential Benefits

Participation in this study will benefit patients in that they will receive more intense follow-up than would be considered standard of care. At the 6 month visit the patient will be assessed for pain, health and general well-being and will undergo a musculoskeletal function assessment in addition to their standard clinical evaluation. In addition, further assessments will be conducted through the use of the Brief Pain Inventory (BPI), Short Form Musculoskeletal Assessment (SMFA), and the Veterans Rand 12 item Health Survey (VR12).

3. STUDY OBJECTIVES

3.1 Primary Objective

To compare the proportion of deep surgical site infections within 6 months in patients treated with local Vancomycin powders compared to those treated without local Vancomycin powder

3.2 Secondary Objectives

To compare antibiotic sensitivities of the bacteria in the patients who develop surgical site infections in study patients treated with local Vancomycin powder compared to those treated without local Vancomycin powder.

To build and validate a risk prediction model for the development of surgical site infections in patients treated without local Vancomycin powders. Further, to explore whether the effect of local Vancomycin powder is modified by the predicted risk of infection.

3.3 Exploratory Objectives

N/A

4. STUDY OVERVIEW

The study design is a prospective, randomized controlled trial comparing deep surgical site infection rates with and without the use of local Vancomycin powder at the time of fracture fixation. This study design will provide the highest quality evidence to investigate our hypothesis that the use of local Vancomycin powder will be effective at decreasing deep surgical site infection in these at-risk patients. The study population will be patients aged 18 to 80 years of age with high energy fractures to the tibial plateau, or pilon, treated operatively with plate and screw fixation.

Patients will be approached for informed consent as soon as is feasible following determination of eligibility. During the index hospitalization, participants will be asked to provide basic demographic information, health status and function prior to injury. Study injury characteristics will be obtained from the surgeon and the participant's medical record.

Participants will be prospectively followed at 2 weeks, 3, and 6 months post-injury. All follow-up visits will occur in person at the hospital and consist of both a clinical examination and interview.

5. STUDY POPULATION

5.1 Description of the Study Population

Approximately 1000 participants (500 per treatment arm, see power analysis section below) will be enrolled from METRC trauma centers over a 12-month period. Participants will be recruited

during hospitalization for the initial injury. Consenting procedures are described in detail in Sections 8 and 13 of this protocol.

5.1.1 Participant Inclusion Criteria

Inclusion criteria

1. All "high energy" tibial plateau fractures treated operatively with plate and screw fixation. We define "high energy" tibial plateau fractures as patients who are either:
   1.1 Initially treated with an external fixation (with or without limited internal fixation) and treated definitively more than 3 days later after swelling has resolved.
   1.2 Any type I, II, or IIIA open fracture, regardless of timing of definitive treatment.
   1.3 Any tibial plateau fracture associated with ipsilateral leg compartment syndrome fasciotomy wounds.

2. All "high energy" pilon (distal tibial plafond) fractures treated operatively with plate and screw fixation. We define "high energy" tibial plateau fractures as patients who are either:
   2.1 Initially treated with an external fixation (with or without fibula fixation or limited internal fixation) and treated definitively more than 3 days later after swelling has resolved.
   2.2 Any type I, II, or IIIA open fracture, regardless of timing of definitive treatment.
   2.3 Any tibial pilon fracture associated with ipsilateral leg compartment syndrome fasciotomy wounds.

3. Ages 18 to 80 years
4. Patients may have co-existing non-tibial infection, with or without antibiotic treatment.
5. Patients may have risk factors for infection including diabetes, immunosuppression from steroids or other medications, HIV, or other infections.
6. Patients may have a head injury
7. Patients may have a portion of the fixation (e.g. fibula fixation in pilon or percutaneous screws across a tibial plateau fracture) prior to definitive plate fixation, at the initial surgery before randomization.
8. Patients may have other orthopedic and non-orthpaedic injuries.
9. Patients may have pre-existing musculoskeletal injuries, be non ambulators, or have spinal cord injuries.
10. Women and minorities are included.

Exclusion criteria

1. The study injury: tibial plateau, or pilon already infected at time of study enrollment.
2. Patient speaks neither English nor Spanish.
3. Patients who have already had definitive fixation prior to enrollment in the study.
4. Severe problems with maintaining follow-up (e.g. patients who are homeless at the time of

injury or those how are intellectually challenged without adequate family support)
5. Patient allergy, drug administration reaction, or other sensitivities to Vancomycin (such as a history of Redman's Syndrome)
6. Pregnancy
7. The study injury is type IIIB or IIIC open fractures

5.1.3 Co-Enrollment Guidelines

Patients may be co-enrolled in other observational studies as long as this is consistent with local IRB policies. At METRC sites that are participating in the local Vancomycin powder study, patients should be preferentially enrolled in the PAIN study if they are eligible for both studies. If a patient is not eligible for the VANCO or PAIN studies, they may be enrolled into the Oxygen study.

5.2 Strategies for Recruitment

N/A

6. STUDY PROCEDURES

6.1 Screening and Enrollment

6.1.1 Screening

The study population will include patients between the ages of 18 and 80, with high energy fractures to the tibial plateau or pilon, treated operatively with plate and screw fixation will be screened for eligibility at each site by the local Research Coordinator in close collaboration with the surgeon investigators. Screening will typically occur during the initial hospitalization for the study injury. A screening CRF will be completed on every potentially eligible participant and entered into REDCap, the METRC electronic data capture system in order to document screen failures. The study PI and MCC team will be available via email and phone to answer questions regarding study eligibility. Contact information for the PI and alternate contact is available in Appendix A.

6.1.2 Consent and Enrollment

A prototype consent has been prepared for the local Vancomycin powder study and is attached in Appendix D. Individual sites may add material but may not delete material thought to be necessary for informed consent. Clinical sites may reformat and reword information to conform to their local requirements. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the signed

consent forms will be given to the patient, and this fact will be documented in the patient's record.

Once eligibility has been confirmed, the informed consent process will be completed by the Research Coordinator and the attending surgeon. Patients will be approached about potential participation in the study as soon as is feasible following determination of eligibility.

Participants will be approached and given the opportunity to enroll during their initial injury treatment. For the high energy tibial plateau and pilon fractures, the definitive treatment is typically delayed for roughly 1-2 weeks to allow swelling at the surgical site to resolve before proceeding for definitive fixation. This allows significant opportunity to enroll the patient during this window. Patients often will have time to discuss the study with others prior to making a final decision to participate. Patients and their families will be provided with a pamphlet describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate. Consent will be obtained in accordance with principles of GCP and ICH guidelines.

For the rare case with an open fracture type that the surgeon deems the wound is clean enough for definitive fixation at the time of initial treatment, the patient may still be enrolled in the study. These patients will be enrolled at the time of initial trauma. This patient group represents a small fraction of the open fractures, which themselves are a small subset of the overall group.

At high energy trauma centers such as those participating in the study, some percentage of the patients will be eligible for the study but will not be able to consent due to traumatic brain injuries, intubation, or for other reasons related to their injury. We will consent these patients using the individuals' legally authorized representative. The process for obtaining consent for surgery or study participation varies based upon the state the patient is being treated within, and as such the details of this process will be guided by the standard practice of the local IRB.

All study materials will be provided in both English and Spanish.

Following completion of informed consent, the participant information will be entered into REDCap where a study number will be assigned and final eligibility criteria confirmed.

6.1.3 Assessing Capacity to Consent and Consenting a Proxy Respondent

By virtue of the types of injuries studied (resulting from high energy mechanisms such as high speed motor vehicle crashes, high falls, and blast injuries) it is expected that a large proportion (> 15%) to have an associated traumatic brain injury which my render them unable to provide consent for the study. It will be important not to exclude these patients from the study, as it would significantly reduce our ability to produce generalizable knowledge. These patients are at

no greater risk of adverse consequences by virtue of their participation in the study, and should be given the same opportunity to participate.

Whenever possible, the patient him or herself (as opposed to a proxy) should be consented. Prior to initiating the consent process, the Research Coordinator will contact the patient's Physician for confirmation that the patient has the ability to understand the relevant study information and communicate and maintain a choice. If the physician indicates that the patient lacks the capacity to consent the legally authorized representative (LAR) will be contacted.

The research staff will endeavor to answer all questions posed by the patient and his/her family to ensure their understanding of the protocol. A limited number of questions will be asked of all patients after they are introduced to the study and have reviewed the consent form. These questions assess the person's understanding of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation. A formal comprehension test may be utilized, or comprehension will be assessed by the person(s) obtaining the consent. A template for a comprehension test is provided in Appendix E.

The Research Coordinator will ask the questions and determine the appropriateness of the responses. If the Research Coordinator is at all unsure about the patient's ability to consent s/he will consult with the study site PI.

A legally authorized representative (LAR) with reasonable knowledge of the potential participant will be approached to consent on the patient's behalf if one of the following is true:

- The patient is unresponsive (and likely to remain unresponsive during the study).
- The patient cannot adequately answer at least 2 questions and it is determined that the patient's level of cognition is not likely to change before surgery.

The choice of LAR will follow standard procedures. The following with be approached in this order of priority:

- Legal guardian
- Proxy (health care agent) named in an advance directive or durable power of attorney for health care;
- Family member or other surrogate identified by the state law on health care decisions.

Guidance will be provided to assist the LAR in making the consent decision. They will advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in mind. They will be asked to carefully

consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.
Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.

6.2 Baseline Data Collection

Once consented into the study, baseline data regarding participant characteristics, injury characteristics, fracture classification and medical history/co-morbidities will be collected and entered into the REDCap data collection system. Characteristics about hospital course and treatment received will also be collected. A brief interview will be conducted with the participant or his/her surrogate.

Blood sampling across the study will occur as performed at all institutions with respect to standard clinical care per institutional practice. This typically includes pregnancy tests when appropriate, serum creatinine, and complete blood count at baseline. The labs may or may not include tests for fungi. We will also pilot test Vancomycin levels within 24 hours of placement of Vancomycin powder in the operating room for the first 30 participants at the main study institution, the University of Maryland, Baltimore (PI site to which this FDA approval was given). As discussed in more detail in section 7 below, it is anticipated that the system levels will be undectable or clinically insignificant based on prior literature [98]. Any adverse events identified over these samples will be reported to the IRB, the FDA, and the rest of the participating sites. These data will be collected in RedCap and will be reviewed as indicated, by the medical monitor (identified below) for the study.

All labs drawn at the sites will follow each institutions standard of care procedures. We will not utilize a central laboratory for testing in this study. We will, however, request CAP/CLIA information for all participating sites to ensure that each lab attests to adhering to standard testing methodology.

To comply with the FDA Annual Reporting requirements, and because the METRC Coordinating Center will not be providing the vials of vancomycin powder to clinical sites, we will also collect the name, strength, manufacturer and back number for every vial of vancomycin used in this study.

6.2.1 Medical Record Review

- Circumstances and Type of Injury
- Other Injuries

- Mode of Transport
- Length of time in ICU
- Discharge Disposition
- Antibiotic Use

6.2.2 Clinical Assessment

- Side of Injury (R/L)
- AO/OTA Classification
- Gustilo Type
- Tscherne Classification
- AP and Lateral x rays

6.2.3 Participant Interview

- Medications taken prior to Injury
- Co-morbidities
- Health Insurance
- Height and Weight
- Demographics (age, gender, race/ethnicity, education)
- Income
- Usual Major Activities Before Injury
- Job Characteristics
- Current Military Service
- Job Motivation
- Smoking History
- Previous Injuries and Pain
- Marital Status and Social Support

6.3 Participant Follow up and Data Collection

6.3.1 Follow-up Visit Schedule

Participants will return for follow-up visits at 2 weeks, 3, and 6 months. The two-week visit will be determined using the date of definitive fixation. Participants will be expected to begin follow up 2 weeks post-definitive surgical fixation for their study injury. At each follow up visit, participants will undergo a clinical evaluation by the treating surgeon and be interviewed by the Research Coordinator.
Each visit will have an interval of time surrounding the ideal date for the visit during which the visit may be completed and the data included in the trial database as defined per METRC standard operating procedures.

6.3.2 Clinical Assessments

- Diagnosis of infection and detailed assessment of evidence of infection
- Complications (type, severity, treatment)
- Wound Healing
- Antibiotic Use
- Fracture Healing
- Pain

6.3.3 Participant Interviews

- Re-Hospitalizations
- Self reported pain (6 months only)
- Brief Pain Inventory (6 months only)
- Health Related Quality of Life (VR-12) (6 months only)
- Short Musculoskeletal Function Assessment (SMFA) (6 months only)

6.3.4 Retention

Every effort will be made to retain participants in the study. The study participants will receive an honorarium in recognition of their time and effort. $**50** will be given for completing the **6** month visits in appreciation for their time and effort. We will also keep participants engaged through use of study updates on the METRC webpage and distribution of follow-up reminders and trinkets imprinted with the study logo.

6.3.5 Final Study Visit

Participants will complete the study at month 6. This final visit will occur in the clinic and will include the patient interviews and clinical assessments as identified above.

Any ongoing SAEs will be followed to resolution.

6.3.6 Early Termination Visit

Should a participant terminate the study prematurely, if at all possible, all procedures required at the 6 month visit will be performed at his/her final visit.

6.4 Study Endpoints

6.4.1 Primary Endpoint

The primary endpoint will be the presence of clinically significant surgical site infection (SSI) in the first 26 weeks after surgery, as determined by CDC guidelines [24,34,51]. These guidelines are described above in detail related to study outcomes.

Wound characteristics will also be evaluated using the ASEPSIS score [15,16,84,85]. This system has also been previously described.

For each patient who is determined to have an infection, the treatment will also be recorded. We will define deep infections as those that require operative treatment, and superficial infections as those that are treated without operative intervention.

6.4.2 Secondary Endpoints

Secondary endpoints include culture data in the group that becomes infected. All deep surgical site infections will have sterile intraoperative wound cultures taken, as is currently performed in routine clinical practice. Sensitivities of the isolated bacteria, which are also determined routinely in current clinical practice, will be recorded for analysis. We will describe the type of antibiotic resistance experienced in both groups as described in the outcomes measures described in the protocol summary.

7. STUDY TREATMENTS

In extremity wounds, a typical local dose would be 1000 mg of Vancomycin powder placed into the wound at time of closure. All other components of the surgery would be per routine protocol at the sites. Previous data indicates that the systemic load from this amount will likely be very low [97,98,99,100]. The typical IV dose is 1000mg twice a day (often for 6 or more weeks if the patient has an infection), so this one time local dose is a relatively small amount of the drug compared to what is typically used in systemic IV therapy.

Most orthopaedic trauma surgeons are already familiar with using sterile Vancomycin powder in the operating room as it is used to make antibiotic beads and nails. The powder comes sterile and the hospitals are very familiar with storage, handling and all other aspects of managing the device. The dose used for this study will be (1000mg) placed right before wound closure.

Both groups will otherwise receive standard care, including prophylactic intravenous antibiotics,

and all other aspects of care that are currently standard for each surgeon and anesthesiologist at each institution. Intravenous Vancomycin can be given as IV prophylaxis if that is the center's protocol for an individual patient. After consultation with multiple infectious disease specialists it appears the risk of renal (or other) toxicity from simultaneous IV and local powder application of Vancomycin is extremely unlikely. Prior studies on systemic levels when using local Vancomycin powder demonstrated an undetectable level in 80% of the patients, and a low level (average 1.6 μg/ml) in 20% of the patients [98]. Local application of Vancomycin powder is very unlikely to increase the risk of Vancomycin side effects. Additionally, in current clinical practice much larger doses of local Vancomycin powder are placed in beads repeatedly during serial irrigation and debridements while patients receives IV Vancomycin for weeks at a time without any known consequence. In this group, serum levels of Vancomycin are also in the low range [103.] For these reasons, the study allows the use of Vancomycin for prophylaxis if that is a center's practice. Whatever antibiotic prophylaxis protocol is used at the site, it should be applied consistently in both the treatment and control group. It would not be appropriate to change the IV prophylaxis choice based on which treatment group that patient was assigned. No changes should be made to routine care based on allocation to the treatment or control group.

Treatment Crossover

Cross-over from one treatment arm to another should be very rare. Cross-over should only occur if for some reason the surgical team determined the local Vancomycin powder could not be placed or if the Vancomycin powder is not available to be placed, both of which would be extremely unusual. As patients will not know which treatment group they are in prior to surgery, there is no chance that they will elect to switch groups based on the outcome of the randomization. The only likely crossover is study error where an investigator forgets to place the local Vancomycin powder in a patient assigned to the treatment group. The rate of this occurrence should be very low.

7.1 Study Treatment #1

7.1.1 Description of treatment

Treatment Group (Local Vancomycin Powder):

Participants in the treatment group will receive a maximum dose of 1000mg of Vancomycin powder in their wound bed, which is placed right before wound closure. Vancomycin powder may be combined with normal saline as per clinical practice at the participating institution.

In addition, participants in this group will receive standard of care treatment for their injury, to include all institution specific standard treatment (prophylactic and otherwise) for preventing and treating infection.

7.1.2 Potential Risks and/or adverse effects

The risks of giving antibiotic powder are increased for participants who have a known allergy to the drug. In addition, there is increased risk for participants who are susceptible to local toxicity to the drug. Additionally there is the risk that the technique may actually increase the risk of infection through some unknown mechanism or create some other as yet unanticipated clinically significant problem.

The typical risks of any fracture surgery include bleeding, infection, malunion, nonunion, and neurovascular injury are inherent risks the operative procedures involved and do not differ from the standard of care.

Any time information is collected for a study there is a small risk of breach of confidentiality. However, this risk is not greater than the risk that already exists in clinical settings when handling medical data.

7.2 Study Treatment #2

7.2.1 Description of treatment

Control Group (Standard of Care):

Participants in this group will receive standard of care treatment for their injury, to include all institution specific standard treatment (prophylactic and otherwise) for preventing and treating infection. Participants in this group will not receive local Vancomycin powder.

7.2.2 Potential Risks and/or adverse effects

The typical risks of any fracture surgery include bleeding, infection, malunion, nonunion, and neurovascular injury are inherent risks the operative procedures involved and do not differ from the standard of care.

Any time information is collected for a study there is a small risk of breach of confidentiality. However, this risk is not greater than the risk that already exists in clinical settings when handling medical data.

8. ASSESSMENT OF SAFETY

The study will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the "Common Rule", shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of "unanticipated problems" involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head.

The medical monitor (MM) is responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of Serious Adverse Event reports; resolving safety issues; and interacting with Principal Investigators.
Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.1 Definitions

8.1.1 Adverse event

Any untoward or unfavorable medical occurrence in a human subject, including abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease temporally associated with the subject's participation in the study, whether or not considered related to the subject's participation.

8.1.2 Unanticipated problem

Any incident, experience, or outcome that meets all of the following criteria:

(1) is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the patients eligible for the study.

(2) is related or possibly related to treatment/procedures under study; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study procedures or treatments.

(3) suggests that the participation in the study may place subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Please note that not all adverse events are unanticipated problems and only some unanticipated problems are in fact adverse events. For instance, if a laptop containing study data is stolen, this is an unanticipated problem but it is not an adverse event since it is not an untoward or unfavorable medical occurrence in a human subject

8.1.3 Serious Adverse Event

A serious adverse event is defined as:

1. Death
2. Allergic or other reaction that is thought to be due to the Vancomycin powder
3. Other events that are unexpected AND serious AND related or possibly related to the use of Vancomycin for the study

8.2 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

8.2.1 Methods and Timing of Assessment

Adverse events may be discovered during regularly scheduled visits or through unscheduled patient contacts between visits. Adverse events related to study procedures will be assessed during the index hospitalization and at each study visit. They will be recorded on study data forms whether or not they are thought to be associated with the study.

8.2.2 AE/SAE Grading and Relationship Assignment

Adverse event grading: Adverse events will be graded using standard criteria. Relationship of event to the study procedure will be determined by the study physician.

GRADE 1 (Mild) Transient or mild discomfort (< 48 hours); no medical intervention/therapy required

GRADE 2 (Moderate) Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 (Severe) Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible

GRADE 4 (Life-threatening) Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Relationship Assignment The relationship of the adverse event to participation in the study will be assessed as either:

Definitely related
Probably related
Possibly related
Unlikely related
Unrelated

8.2.3 Recording and Documentation

Sites will maintain source documents including but not limited to (laboratory and radiology reports, clinical notes and discharge summaries). After review of initial and final reports by the medical monitor, the events may be reclassified at their discretion.

8.2.4. Management of Adverse Events

Adverse Events and Serious Adverse Events will be managed according to protocol guidelines. If specific guidelines do not exist, AEs/SAEs will be managed according to the medical judgment of the treating physician.

8.3 Adverse Event Reporting Procedures

8.3.1 Local Reporting Requirements.

Study sites must always follow and comply with their own local institution's adverse event reporting requirements, which may differ from those adopted by the local Vancomycin powder Study. Depending on the local requirements, a site may report events locally and not report those events to the METRC Coordinating Center. Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

8.3.2 SAE and Unanticipated Problem Reporting Requirements

All Serious Adverse Events that are Unexpected AND related or possibly related to the study must be reported to the Medical Monitor and METRC Coordinating Center within 72 hours of

being made aware of the event. In addition, all SAEs related to use of study medications would be reported to the individual manufacturers to contribute safety data for these drugs, as well as to the FDA via the MedWatch voluntary reporting mechanism using form FDA 3500.

In addition, Unanticipated Problems (UPs) that are not adverse events must also be reported to the METRC Coordinating Center within 14 calendar days after the event has been discovered. SAEs/UPs will be reported to the METRC Coordinating Center by entering the SAE/UP form into REDCAP. REDCap is programmed to automatically send an email to the Coordinating Center for both SAEs and Ups, and to the Medical Monitor in the case of an SAE.

The Medical Monitor for this study is:
Mark Swiontkowski, MD, FACS
Department of Orthopedic Surgery
2450 Riverside Ave., R200
Minneapolis, MN 55454
Telephone: (612) 273-7951
Fax: (612) 273-7959
E-mail: swion001@umn.edu

8.3.3 METRC Coordinating Center Reporting Responsibilities

As appropriate and per METRC policies, the Coordinating Center will send a copy of each report received about an event judged reportable to all clinical sites, with instructions for each to forward the report to their IRB.

Copies of the report will also be sent to the DoD, the Study PI, and to the Medical Monitor. The MCC will maintain a list of such events for reporting and review at Steering Committee meetings.

8.3.4 Department of Defense Reporting Requirements

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

(1) The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

(2) Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

(3) All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@.amedd.army.mil), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

(4) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

(5) Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

(6) Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

(7) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

(8) The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

Unanticipated problems involving risk to volunteers or others, serious, unexpected adverse events related to participation in the study and all volunteer deaths related to participation in the study will be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be

sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RPH, 504 Scott Street, Fort Detrick, Maryland 21702-5012

8.4 Reporting Pregnancy
N/A

8.5 Type and Duration of the Follow-up of Participants After Adverse Events

Study patients who experience an SAE will be followed until resolution of the event, and a final report will be submitted to the medical monitor, the FDA, and the coordinating center.

8.6 Modifications of Study Agent(s)/Intervention(s) for a Participant
N/A

8.7 Halting Rules for the Protocol

If the treating surgeon determines that the patient is medically contraindicated to receiving the Vancomycin powder for any reason, they should treat the patient appropriately and not pursue the application of the study specific treatment arm.

8.8 Stopping Rules for an Individual Participant/Cohort

The DSMB will review the overall progress of the trial in terms of recruitment and data quality and makes a formal recommendation to the DOD at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications or be stopped.

8.9 Premature Withdrawal of a Participant

Withdrawal from the study will be overseen by both the Coordinating Center, and individual institution to which the participant is enrolled. However, once surgery has been completed; the treatment arm of the study will be final so it is not possible for the subject to withdraw from this portion of the study. However, the patient could withdraw from the study by failing to follow- up. In the event that participants fail to follow up, research staff will attempt to contact them to determine whether or not they are having problems. If participants choose to withdraw after they have received treatment they will be made aware that this choice will not affect their current and future care at the study site but they will be asked to communicate with the study team any issues they might have related to their initial injury. Patients will not be removed for failure to follow post-operative instructions, non-compliance with treating instructions, or any other deviations from ideal clinical pathway. These deviations are common in clinical medicine and therefore are not grounds for removal from the study.

Only loss of funding or behavior by the patient (e.g. threatening of clinical staff) would cause termination of the clinical relationship would require withdrawal from the protocol. Neither is anticipated to be common but participants will be made aware that termination could occur and that the research team will communicate any changes associated with the study that may affect them and their participation. If study termination needs to occur due to loss of funding, all participants currently enrolled will be followed to completion and no new participants would be enrolled. Communication of this would occur to the satellite sites via the coordinating center.

8.10 Replacement of a Participant Who Discontinues Study Treatment

N/A

9. MONITORING

9.1 Site Monitoring Plan

The METRC Coordinating Center will be responsible for site monitoring consistent with ICH/FDA guidelines. Monitoring will include a combination of remote and on-site visits of participating clinical research sites to review the individual subject records, including consent forms, case report forms, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed.

The site PI will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the DOD, the Office for Human Research Protections (OHRP), or other regulatory authorities for confirmation of the study data.

9.2 Safety Monitoring Plan

9.2.1 Safety Review Plan by the DSMB

An independent Data and Safety Monitoring Board (DSMB), appointed by DOD, is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality. An interim analysis will occur after **33% of** patients have been followed for **6** months.

The DSMB is a multidisciplinary group with a written charge provided by METRC and DOD. The DSMB will meet in person to review the protocol. After the trial commences, the DSMB

meets twice a year to review data or other issues. The DSMB may request more frequent meetings if necessary to fulfill it charge. It may also request additional safety reports on a more frequent basis. For example, all serious adverse events (SAE) are reported to the DSMB for their consideration and recommendations as they occur.

At its first meeting the DSMB will review definition of all outcomes, adverse events and serious adverse events and revisions to the protocol made as appropriate. Summary data on adverse events (together with study outcomes) will be monitored by the DSMB at its semiannual meetings or more frequently, as needed. These summaries will include analyses comparing rates of adverse events by blinded treatment group, by clinic, or in other subgroups requested by the DSMB.

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events, for transmission to the IRBs at each of the study centers. Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol, which might entail risk to participants, must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met.

The DSMB will review semi-annual reports by masked treatment groups of the primary and secondary outcomes as well as all adverse events that are not identified as outcomes per se. Interim data on safety measures requested by the DSMB are reviewed at each of the scheduled semi-annual full meetings. Analyses will be prepared comparing rates of adverse events by treatment group, by clinical center or by other subgroups as requested by the DSMB. Serious adverse events will be reviewed by the DSMB as they occur with the option of a teleconference if any DSMB member requests

10. STATISTICAL CONSIDERATIONS

10.1 Overview and Study Objectives

Again, the primary objective of the study is to investigate if local Vancomycin powder reduces deep surgical site infection after operative treatment of fractures at risk for surgical site infection, as this is a common problem encountered in the treatment of military injuries. The study design is a prospective, randomized controlled trial comparing deep surgical site infection rates with and without the use of local Vancomycin powder at the time of fracture fixation. The study population will be patients aged 18 to 80 years of age with high energy fractures to the tibial plateau or pilon, treated operatively with plate and screw fixation.

10.2 Sample Size Considerations

We based the sample size on a two-group comparison of proportion of deep surgical site infection between the treatment groups during the first 6 months of treatment. In our prior oxygen study, 250 patients draw from a similar patient population as that proposed yielded a 3-month deep infection risk of 11.5% [72]. As discussed in section 1.5, rates of deep surgical site infection after these fractures has varied considerably in previous studies with both higher and lower rates being reported in what are typically retrospective studies. We argue that our existing prospective data in an almost identical patient population, with the same fracture types, using the same primary outcome measure should yield a reasonably accurate estimate of anticipated infection rate in the proposed study group.

Therefore, in our sample size calculations, we assumed that control arm would have an infection probability of 11%. Using a two-sided test 0.05 level test of no treatment difference, we need 464 patients to have 80% power to detect a 5.1% absolute reduction (45% relative reduction) in the probability of infection by 6 months. The previous spine literature has shown much larger relative reduction in surgical site infection so this is a conservative estimate in that regard.

We plan one interim analysis (after a third of the patients have been followed for 6 months) using an O'Brien-Fleming stopping boundary. We inflate the sample size by 1% in order to preserve the type I error. We also conservatively inflate the sample size by 5% to account for loss to follow-up.

Sample Size

Based on the above considerations, the targeted sample size for the study is 500 fractures per study arm.

10.3 Randomization

Randomization Methodology. Patients will be randomized electronically by the online Data Management System maintained at the Coordinating Center at Johns Hopkins School of Public Health. Patients will be randomly assigned (within center) in a 1:1 ratio to either treatment group (local Vancomycin powder) or control group (no local antibiotics). Randomization will occur at the time of the surgery so that the patient will not be aware pre-operatively or post-operatively which treatment group he or she is in.

Block randomization will be used to ensure equal distribution of treatment and control patients within the two fracture types (tibial plateau, and pilon fractures). Participants who refuse randomization will not be eligible for the study and will receive the control treatment.

Blinding of Randomization. Due to the nature of the study it will not be possible to blind the treating surgeon regarding which treatment the patient received. There will be no way to examine the patient or the radiographs to determine if the patient received the local Vancomycin powder. As the primary outcome measure is deep surgical site infection requiring return to the operating room, we believe that the surgeon's lack of blinding is less problematic in this case compared to an outcome variable that required more subjective evaluation such as superficial infection. Further, a standardized METRC infection CRF was designed during this study to record standard data (culture data, wound characteristics) to guard against any possibility of false positives.

Additionally, we will blind all of the data from the statistician prior to the preparation of reports when blinding is no longer possible, as is the standard practice at the data coordinating center at Johns Hopkins School of Public Health. All analyses will be done at the data coordinating center (which is not a clinical center) to help reduce risk of bias in the analysis.

10.4 Missing Data and Measures to Minimize Bias

Missing data is a serious concern that complicates the interpretation of the study results. We will address this issue from both a study conduct and analysis perspective. Regarding study conduct, we will:

1. Limit participant burden and inconvenience in data collection
2. Select high quality investigators
3. Provide pre-study training of investigators as well as on-study reinforcement
4. Reimburse investigators based on follow-ups completed not on per-patient basis.
5. Monitor and report missing data rates during the study
6. Emphasize the importance of full participation in the study during the consent process.
7. Collect information on the reasons for missing data.
8. Actively engage participants and educate them about the importance of participation
9. Hold regular Protocol Committee meetings to discuss strategies for follow-up
10. Set targets for acceptable rates of missing data and terminate sites not meeting targets.

As with most prospective studies, missing data will be unavoidable (even with excellent follow- up). Since the informative nature of missing data cannot be verified from the observed data, we will adopt a sensitivity analysis framework for reporting results. We will analyze data under a variety of modeling assumptions regarding how strongly the missingness mechanism is related to outcomes [65].

10.5 Planned Interim Analysis

An independent Data and Safety Monitoring Board (DSMB) is responsible for approval the protocol for this trial and for monitoring the accumulated interim data as the trial progresses to ensure patient safety, review efficacy, evaluate recruitment, and assess overall data quality. After the trial commences, the DSMB will meet twice per year to review data and other trial-related issues. The DSMB may request more frequent meetings if necessary to fulfill its charge.

The DSMB will review one planned interim analysis of the primary outcome measure. O'Brien- Fleming stopping guidelines for efficacy will apply. The interim analysis will occur when approximately 1/3 of the patients (roughly 330) will have 6-month outcome data. At the end of each meeting, the DSMB will make a formal recommendation as to whether the trial should continue un-modified, continue with protocol modifications, or to be stopped.

10.6 Analysis Plan

<u>Specific Aim 1</u>:

Statistical analyses will follow the intent-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized.

Treatment effects for binary endpoints (e.g., infection) will be estimated using a two-group binomial comparison of proportions; 95% confidence intervals for the absolute risk difference and relative risk will be reported. Tests on the null hypothesis of no treatment effect will be based on both a Chi-squared test and a Fisher's exact test – p-values will be reported.

Treatment effects for continuous endpoints will be estimated using a two- group comparison of means; 95% confidence intervals for the difference in means will be reported. Tests on the null hypothesis of no treatment effect will be based on both a t-test and a Wilcoxon rank-sum test and p-values will be reported.

For both binary and continuous outcomes, regression modeling may be employed if concerns about confounding arise, due to imbalances between treatment groups with respect to key prognostic baseline covariates. Random effects regression modeling may also be employed if concerns regarding the clustering of outcomes within surgeons or

centers emerge.

Specific Aim 2:

For patients who are infected, we will compute a one-sided, 95% lower confidence interval for the difference in antibiotic sensitivity to between treated and control. We will compare this difference to a 10% non-inferiority margin.

Specific Aim 3:

We will build a risk prediction model for infection using data from our previous oxygen trial and a training sample from the control group of the proposed trial to estimate the parameters of a multivariate logistic regression model. Demographic and injury characteristics will be included as covariates in the model. The predictive accuracy of the model will be assessed by computing the estimated risk of infection on a test sample of patients from the control group of the proposed trial and calculating the area under the receiver operating characteristic curve.

After building the risk prediction model, we will compute a risk prediction score for each patient in the trial and assess, via interaction terms in a logistic regression model, whether the effect of local Vancomycin powder on infection is modified by risk score.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

Quality Control (Q/C) and Quality Assurance (Q/A) procedures that apply to all studies are outlined in the METRC Manual of Operations (MOP). A certification process (also outlined in the MOP) will be used as a basis for training and certification of the study personnel involved in data collection. In addition to consortium wide training and certification procedures, additional requirements may be added based on the nature of the study. Ongoing data edits and audits will be performed to ensure collection of quality data. The continuous and timely flow of data from the centers to the MCC is an essential prerequisite for maintaining data quality.
Monthly enrollment reports will be distributed to each center that will summarize recruitment, data completion and timeliness of data entry. These reports will also include a set of queries generated by REDCap and sites will be asked to address these queries within 10 business days.

11.2 Training and Certification of Centers

All participating centers together with their respective study personnel will undergo certification that included training, local site IRB, and a knowledge assessment on the study design and procedures.

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 IRB/Ethics Committee

IRB approval will be obtained from the MCC at Johns Hopkins Bloomberg School of Public Health, the DoD, and each participating clinical site according to METRC policies and procedures. Sites that recruit patients will submit METRC study recruitment materials to their organization's IRB prior to use at that facility.
Sites must provide the Coordinating Center with a copy of the initial IRB approval notice and subsequent renewals as well as copies of the IRB approved consent statements.
No site can begin work related to this study until the site has been certified by the MCC in accordance with METRC policies and procedures.

12.2 Exclusion of Women, Minorities, and Children (Special Populations)

The proposed study anticipates recruiting a significant proportion of racial/ethnic minorities (African-Americans, Asian-Americans and Hispanics) as well as non-Hispanic white subjects. The study will not include children or prisoners. The study will also exclude pregnant women.

12.3 Participant Confidentiality

It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, ICH Guidelines, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient's anonymity be maintained in their data submission to the Data Coordinating Center.

Patients will be identified only by an identification code but not by their name, SSN, or hospital medical record number. Study Site Investigators will maintain a separate confidential enrollment log, which matches identifying codes with the patients' names and addresses available only to local clinic staff certified by the MCC to participate in the study.

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the sponsor (MCC), IRB, DOD, or DSMB. Consent procedures and

forms, and the communication, transmission and storage of patient data will comply with individual site IRB and DOD requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

12.4 Study Discontinuation

Participants will be informed that they may discontinue the study at any time, for any reason. They will be assured that the medical care which they receive at the participating facility will not be affected should they elect to discontinue participation in the study.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Instructions concerning the recording of study data on case report forms will be provided by the MCC. Each study site is responsible for transmitting the data in a timely fashion.
The research coordinators at each site will obtain the information necessary to complete the case report forms (CRFs) from several sources including but not limited to, the patient's medical record, clinical evaluations and patient interviews. These forms will NOT contain the patient's name, SSN, or hospital medical record number; they will be identified only by a unique patient-specific study number.

The Site Research Coordinator will enter non-personally identifiable information into a central and secured web-based data management system being implemented for all Consortium studies, known as REDCap. This data management system has incorporated state-of-the-art features for electronic data collection and is configured in accordance with best practices for information technology and research data management.

All research data, in hard copy or electronic form, will be stored and managed in a secure manner following applicable federal regulations and ICH guidelines and according to institutional policies and practices. Hard copy documents containing subject data, patient identifiers and contact information will be stored in secure, locked containers (file cabinets, drawers, etc.) in accordance with standard document management practices.

At all times only MCC-certified key personnel specifically designated and authorized by the Principal Investigator shall have access to any research related documents, including electronic data and medical records. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct. This information will be available for audit by study monitors and representatives of the local IRB, the MCC, the DOD, and the OHRP.

13.2 Data Capture Methods

Data will be collected in real time by the investigator or study coordinator directly on paper Case Report Forms (CRFs), which will serve as source documents for the study. Source documents, which will include both the CRFs and other supporting medical records (e.g laboratory & radiology reports, clinical notes and discharge summaries), will be signed by PI, other site Investigator, or Research Coordinator as indicated in the CRF instructions. The Research Coordinator, or MCC-certified staff member working under the supervision of the research coordinator, will enter the data from the CRFs into the REDCAP database.

13.3 Types of Data

Data will include medical and surgical histories, laboratory reports (as obtained as part of standard clinical care by site), radiology reports, clinical evaluations, adverse events and patient interviews.

13.4 Source Documents and Access to Source Data/Documents

Source documents including CRFs, laboratory results (as obtained as part of standard clinical care by site), patient surveys, medical records, etc. will be maintained at the site and will be made available to study monitors, and representatives of regulatory agencies including the MCC, DOD, IRB, and OHRP.

13.5 Study Records Retention

Study records will be maintained in accordance with current ICH guidelines. Data will be maintained for five years following the end of research-related activities. At the end of this period, each site will provide the Coordinating Center a signed verification that these data have been destroyed.

13.6 Protocol Deviations

Records of protocol deviations will be noted on the Protocol Deviation CRF (AF05) with the reason for the deviation recorded, as well as any action taken to mitigate the deviation. This information will be entered into REDCap. These records will be provided to the site's IRB in accordance with local reporting requirements and be made available to study monitors.

14. PUBLICATIONS POLICY

Publications will be written in accordance with the METRC publication policy (available on the METRC website: www.metrc.org).

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17. APPENDICES

APPENDIX A: STUDY CONTACT ROSTER

Principal Investigator (Protocol Chair)		**METRC Coordinating Center Study Principal Investigator**
Robert V. O'Toole, MD University of Maryland, Baltimore Department of Orthopaedic Trauma 22 S. Greene St. Baltimore, MD 21201 Phone: 410-328-6292 E mail: rotoole@umoa.umm.edu		Renan Castillo, PhD Johns Hopkins Bloomberg School of Public Health Dept. Health Policy and Management 624 N. Broadway Room Baltimore MD, 21205 Phone: 410-614-4024 Email: rcastill@jhsph.edu

DOD Program Officer Joseph C. Wenke, PhD Program Manager United States Army Institute of Surgical Research 3400 Rawley E. Chambers Avenue, Bldg. 3611 Fort Sam Houston TX, 78234-6315 Phone: 210-916-3742; Cell: 210-288-2431 Email: Joseph.Wenke@us.army.mil **Medical Monitor** Marc Swiontkowski, MD Professor of Orthopaedic Surgery University of Minnesota 2512 South 7th Street Suite R200 Minneapolis, MN 55454 Phone: (612) 273-,0 Email: swion001@umn.edu		**METRC Coordinating Center** **Director of Protocol Development** Lauren E. Allen, MA Johns Hopkins Bloomberg School of Public Health Dept. of Health Policy and Management 415 N. Washington Street Baltimore MD, 21231 Phone: 410-955-2492 Email: lallen19@jhu.edu **METRC Coordinating Center Study Manager** Tara J. Taylor, MPH Dept. of Health Policy and Management 415 N. Washington Street Baltimore MD, 21205 Phone: 410-614-6081 Email: ttaylo56@jhu.edu **METRC Coordinating Center** **Director of Data Management** Anthony Carlini, MS Johns Hopkins Bloomberg School of Public Health Dept of Health Policy and Management 415 N. Washington Street Baltimore MD, 21205 Phone: 410-502-8455 Email: acarlini@jhu.edu

APPENDIX B: PROTOCOL COMMITTEE

Robert V. O'Toole, MD (Study PI)
University of Maryland Medical Center

Michael Bosse, MD
Carolinas Medical Center

Manjari Joshi, MD
University of Maryland Medical Center

Ellen MacKenzie, PhD
Johns Hopkins Bloomberg School of Public Health

David Hak, MD
Denver Health & Hospital Authority

Daniel Chan, MD
Florida Orthopaedic Institute/Tampa General & St. Joseph's Hospitals

Joshua Langford, MD
Orlando Regional Medical Center

Debra Sietsema, PhD, RN
Orthopaedic Associates of Michigan
Spectrum Health

Hassan Mir, MD
Vanderbilt University Medical Center

Nalini Rao, MD
University of Pittsburg

Renan Castillo, PhD
Johns Hopkins Bloomberg School of Public Health

Amanda Holmes, MS
University of Maryland Medical Center

Daniel Scharfstein, ScD
John Hopkins Bloomberg School of Public Health

Lauren E. Allen, MA
Johns Hopkins Bloomberg School of Public Health

Tara Taylor, MPH
Johns Hopkins Bloomberg School of Public Health

Dean Tsukayama, MD
Hennepin County Medical Center

Clinton Murray, MD
Brooke Army Medical Center

Zachary Roberts, MD
University of Oklahoma/OU Med Center

Joseph Hsu, MD
Carolinas Medical Center

Matthew Graves, MD
University of Mississippi

Study website: www.metrc.org

APPENDIX C: DATA COLLECTION SCHEDULE

Assessment	Base-line	2 Weeks	3mo	6mo
Patient Characteristics				
Demographics (age, gender, race/ethnicity, education)	X			
Income	X			
Usual Major Activities Before Injury	X			
Job Characteristics	X			
Current Military Service	X			
Job Motivation	X			
Smoking History	X			
Previous Injuries and Pain	X			
Marital Status and Social Support	X			
General Injury Characteristics				
Circumstances and Type of Injury	X			
Other Injuries	X			
Medical History				
Medications taken prior to Injury	X			
Co-morbidities	X			
Health Insurance	X			
Height and Weight	X			
Study Injury Characteristics				
Side of Injury	X			
AO/OTA Classification	X			
Gustilo Type	X			
Tscherne Classification	X			
Muscle Injury	X			
Nerve Damage	X			
Soft Tissue Loss	X			
AP and Lateral x rays	X			
Index Hospitalization				
Mode of Transport	X			
Length of time in ICU	X			
Discharge Disposition	X			
Antibiotic Use	X			
Clinical Follow-up Assessments				
Deep Surgical Site Infection		X	X	X

Assessment	Base-line	2 Weeks	3mo	6mo
Complications (type, severity, treatment)		X	X	X
Wound Healing		X	X	X
Antibiotic Use		X	X	X
Fracture Healing		X	X	X
Pain		X	X	X
Self Reported Assessments				
Re hospitalizations		X	X	X
Self reported pain				X
Brief Pain Inventory				X
Health Related Quality of Life (VR-12)				X
Short Musculoskeletal Function Assessment (SMFA)				X

APPENDIX D: CONSENT TEMPLATE

INFORMED CONSENT DOCUMENT

Draft Participant Consent Form

Study Title: Local Antibiotic Therapy to Reduce Infection after Operative Treatment of Fractures at High Risk of Infection: A Multicenter Randomized Controlled Trial

Principal Investigator: Robert V. O'Toole, MD, MS

You are being asked to volunteer to be a part of a research study. Please read this form carefully before you sign it. This consent form explains the research study and your part in the study. If you decide not to participate in this study there will be no impact on your medical care. You can choose not to take part and if you join, you may quit at any time. Ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand. Ask as many questions as needed. All of your questions should be answered to your satisfaction before you sign this form.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

This research is being done to help determine the best treatment for severe lower leg injures like yours. Some broken bone injuries can be more likely to get an infection. It is mostly due to the way they were injured. These injuries are: a break in the top of your tibia (larger bone in your lower leg), or a break in your pilon (break in the bottom part of your tibia (larger bone in your lower leg)).

Surgical site infection in the orthopaedic surgery population is a big public health issue. Wound infections result in both longer length of hospital stay and total cost of care. This study will be using an antibiotic called Vancomycin. This antibiotic is usually given using an injection (intravenous (IV) format).

Some research has been done with spine surgery. The research has shown that by using local antibiotics in the form of a powder sprinkled right in the site of surgery can have a smaller risk for infection later. In these studies there were no reports of problems for participants. Many orthopaedic surgeons are now using this antibiotic powder as part of their

standard clinical practice. We would like to see if this works the same with people who have surgery for a broken leg bone.

This study is funded by the Department of Defense (DOD) and is being carried out in more than 25 major trauma centers across the United States, including four Military Treatment Facilities that are taking care of service members who are injured in the line of duty.

2. WHY AM I BEING ASKED TO PARTICIPATE?

You are being asked to participate in this study because you are between the age of 18 and 80 and you have a severe injury of the lower leg, or ankle. People like you who are being treated at major trauma centers from around the county are being asked to participate. You are one of over 1000 patients we are asking to join this study.

3. HOW LONG WILL THE STUDY LAST?

Your participation in this study will last for 6 months following your injury.

4. HOW DOES THE STUDY WORK?

If you agree to participate in this study, we will fix your broken bone as we normally would. The only change to normal care would be to randomize (this is like the flip of a coin) you to one of two groups.

Group 1 will receive antibiotic (Vancomycin) powder at your surgery site during your surgery in addition to the standard of care antibiotic treatment at your facility (care that would be no different than what you would receive if you were not in the study). If you are in Group 1 you will not be charged for the antibiotic powder.

If you are in Group 2, you will get the standard of care antibiotic treatment at your facility (care that would be no different than what you would receive if you were not in the study).

After your surgery, your care will be exactly the same as if you were not in the study. You will be asked to come back to the clinic and follow up with us at 2 weeks, 3 months, and 6 months after your surgery. These visits coincide with times you would normally come back to see your physician for a check-up. During these visits the following things will happen:

- You will have a physical exam

- Because you are in the study, you will be asked additional questions by a member of the study team. These questions will typically take about 5 minutes of your time and will usually be asked while you are waiting to see your surgeon.
    - We will check to see if you have been re-hospitalized for your injury since your last follow-up visit. If you have, we will gather the details about the hospitalization from your medical record.
    - We will ask you if you have had any problems with your injured leg and if you have been told you have an infection by any of your doctors outside of this facility.
    - You will also be asked if you are taking any kind of medication for any kind of infection.

In addition, at the 6 month study visit we would like to ask you some questions about pain, your health and general well being. These questions are widely used in research and have been found to be useful in finding out how you are doing after your injury. These include the Brief Pain Inventory (BPI), Short Form Musculoskeletal Assessment (SMFA), and the Veterans Rand 12 item Health Survey (VR12). The questions should take you approximately 10 minutes to answer.

5. WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS?

There are standard risks with surgery. These will be explained to you along with your consent for surgery. There are also standard risks associated with receiving any antibiotics. One risk is developing resistance to the antibiotic you will receive. There may also be risks of using Vancomycin in powder form that are not yet known. This use of Vancomycin has not been approved by the FDA, but some doctors use the drug in this manner outside the study. The FDA has permitted this use for this study.

The risk of giving you antibiotic powder is increased for those of you who have an allergy to the drug Vancomycin. In addition, there is increased risk for those of you who are susceptible to local toxicity to the drug. If you have a known risk to antibiotics please talk with your treating surgeon.

Any time information is collected for a study there is a small risk of breach of confidentiality. As described below, your research data will be identified by a unique study number rather than your name and all measures allowed by law to protect your confidentiality will be taken by the research staff.

6. WHAT ARE THE POTENTIAL BENEFITS?

As a result of your participation in this study you will receive more focused clinical follow-up. At your 6 month visit you will be assessed for pain, health and general well-being and will undergo a musculoskeletal function assessment in addition to your standard clinical evaluation. In addition, you will be further evaluated using specific questions related to pain and your activity level (Brief Pain Inventory (BPI), Short Form Musculoskeletal Assessment (SMFA), and the Veterans Rand 12 item Health Survey (VR12).

7. DO I GET ANY PAYMENT FOR BEING IN THE STUDY?

You will receive $50 each for completing the 6 month visit. This payment is in appreciation of your time and effort.

8. ARE THERE ANY COSTS INVOLVED IN BEING IN THE STUDY?

If you are randomized to receive the Vancomycin powder, it will be paid for by the study. There is no cost to you to participate in this study.

9. WILL MY INFORMATION BE KEPT PRIVATE?

The information we collect from you will be kept private to the best of our ability. Your name, birth date, medical record number and any other information that could identify you as an individual will be removed from all study forms. Instead, we will label your forms with a unique study number. The link between your name and your study number will be kept confidential to the greatest extent provided by law. The information collected for the study will be stored in a password protected, HIPAA verified computer database that only authorized members of our research team can use. When we report the results of the study, we will combine the information about you with similar information about hundreds of other people so your individual information will not be identifiable.

All study records will be considered confidential, and your name will not be used in reports or publications.

10. WILL YOU SHARE MY INFORMATION WITH OTHERS?

We will use your information only for the purposes of this study. The data from the study may be published. However, you will not be identified by name. People designated from the institutions

where the study is being conducted will be allowed to inspect sections of your medical and research records related to the study. This includes people designated by The Johns Hopkins Bloomberg School of Public Health who are overseeing this study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

The Department of Defense is providing funding to sponsor this study. Federal or DoD representatives and your local IRB may have access to research records in their role to protect human subjects engaged in research.

11. WHAT ARE MY ALTERNATIVES TO PARTICIPATION?

Your alternative is to not take part in the study. If you choose not to take part, your healthcare will not be affected.

12. WHAT HAPPENS IF I LEAVE THE STUDY EARLY?

Your participation in this study is completely voluntary. You have the right to withdraw from the research study at any time without penalty. Your decision will not affect the medical care you receive. If you decide to stop participating, you should notify the study doctor or the research coordinator at your center.

Your participation in this research study could be ended without your consent if we decide to end the study early. You may also be withdrawn from the study if your injury is not determined to be severe enough for inclusion.

13. WHAT HAPPENS IF I AM INJURED OR BECOME ILL BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or become ill because of your participation in this study, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be billed for any other medical care. If you have any costs that are not covered by insurance, they are your responsibility.

You do not give up any of your legal rights by signing this form. You can seek legal compensation for any injury that may occur to you during the study as a result of an error by a member of the research staff or others.

14. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

- <<insert name>>, the study coordinator at your hospital has discussed this information with you and offered to answer any questions you may have. If you have further questions or get sick or injured as a result of being in this study, you can contact << insert him/her>> at <<telephone number>>. You may also call the Director of the Study at your hospital, <<insert name>>, at <<telephone number>>.

- If you have further questions about your rights as a study participant you can call or contact your local IRB office or the Johns Hopkins Bloomberg School of Public Health IRB Office. The Johns Hopkins Bloomberg School of Public Health is serving as the overall coordinating center for this study that is being conducted in hospitals around the country. Contact the Johns Hopkins IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

- <<insert local IRB contact information here>>

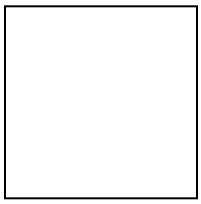
You will receive a copy of this signed consent form.

What does your signature (or thumbprint/mark) on this consent form mean?

Your signature (or thumbprint/mark) on this form means:

- You have been informed about this study's purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

_____	_____	_____	
Print name of Adult Participant	Signature of Adult Participant	Date	Time



Ask the participant to mark a "left thumb impression" in this box if the participant (or participant's parent) is unable to provide a signature above.

_____ _____ _____

Print name of Person Obtaining Consent | Signature of Person Obtaining Consent | Date | Time

APPENDIX E: EVALUTION TO GIVE CONSENT

EVALUATION TO GIVE CONSENT

Procedure: Make a subjective judgment regarding item 1 below. Ask questions 2 through 4. You may select the language to use in asking the questions in order to help the respondent understand them.

1. Is the respondent alert and able to communicate with you?

   Yes ___ No ____ (if condition not likely to change, seek proxy consent)

2. Ask the respondent to name at least one thing that s/he will be asked to do as part of the study.

   *Describe*_____
   _____

3. Ask the respondent to explain what s/he could do if s/he decided s/he did not want to participate in the study.

   *Describe*_____
   _____

4. Ask the respondent to explain what s/he would do if s/he were experiencing distress or discomfort at any time during the study.

*Describe*_____
_____

I hereby certify that the above-named respondent is alert, able to communicate, and able to give acceptable answers to items 2, 3, and 4, above.

_____ _____
Research Coordinator Date

APPENDIX F: BROCHURE INSERT

Be Part of the Local Antibiotic Powder (VANCO) Team!
Help advance limb trauma care through research

What is the Local Antibiotic Powder Study?
Very bad breaks of the lower leg and ankle are difficult to treat and are associated with infection and other complications. The goal of VANCO is to determine whether a higher amount of using local antibiotics in a powder form during surgery can reduce your risk of infection.

Why me?
This VANCO study is funded by the Department of Defense (DOD) and is being carried out in more than 25 major trauma centers across the United States, including four military treatment centers that are taking care of service members who are injured in the line of duty.

You are being asked to participate in this study because you have a badly broken bone in your lower leg or ankle that your surgeon has determined is bad enough to qualify for the study. People with injuries similar to yours who are being treated at major trauma centers from around the county are being asked to participate.

How does the study work?
We will observe the outcomes of your treatment and we will follow your recovery.

After you sign this informed consent and agree to be part of the study, the following things will happen:

- You will be randomized to either standard of care antibiotics or some additional local antibiotic (Vancomycin) powder placed in your surgical wound at the time of surgery to fix your broken bone.
- Information will be collected about your injury and your surgery from your medical record and your surgeon and will be entered into a database by a member of the research team.
- You will receive surgery to treat your injury. You and your surgeon will decide on the best course of treatment.

After your surgery your care will be exactly the same as if you were not in the study. You will be asked to come back to the clinic and follow up with us at 2 weeks, 3 months, and 6 months after your surgery. During these visits the following things will happen:

- You will have a physical exam
- An x-ray will be taken to see how your bone is healing
- You will be asked about any treatment to your leg that you have had other than with your surgeon
- You will be asked if any doctor other than your surgeon has told you that you have an infection in that leg
- You will also be asked if you are taking any antibiotics for any infection.

We will take a look at your surgical site and ask you some general questions about your health. We hope you will consider taking part in the VANCO study. It is a way to be part of a nationwide effort and to help advance limb trauma care for others in the future. Please talk to your doctor about participating, or visit www.METRC.org to learn more.

APPENDIX G: INTERVIEWS

[Will submit SF12, SMFA, BPI to IRB and will attach separately]