AWARD NUMBER: W81XWH-21-1-0833

TITLE: Does Prophylactic Local Tobramycin Injection Lower Open Fracture Infection Rates?

PRINCIPAL INVESTIGATOR: Arun Aneja, MD, PhD

CONTRACTING ORGANIZATION: University of Kentucky, Lexington, KY

REPORT DATE: October 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2023	Annual	01Sep2022-31Aug2023

4. TITLE AND SUBTITLE

Does Prophylactic Local Tobramycin Injection Lower Open Fracture Infection Rates?

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-21-1-0833

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Arun Aneja, MD, PhD
Jeffrey Austin Foster, MD

E-Mail: arunaneja13@gmail.com

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Kentucky Research Foundation
500 S Limestone, 109 Kinkead Hall
Lexington, KY 40526-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: This study addresses the Clinical Trial Award (CTA) focus area of Translation of early research findings under the category of fracture related infection (FRI). Open extremity fractures (OEFs) sustained from traumatic injuries are higher risk for FRI and nonunion due to damage of the soft tissues, impaired bone vascularity and healing, and diminished host defenses against bacteria.

Hypothesis/Objective: This study tests the hypothesis that administering a local dose of tobramycin injection in combination with systemic perioperative intravenous (IV) antibiotic prophylaxis will reduce the rate of FRI one year after OEF fixation surgery. This study will also determine bacterial speciation and antibiotic sensitivity among study patients who develop FRI, as well as nonunion status among all participants.

Specific Aims:
Aim 1: Determine if a local dose of tobramycin (2 mg/mL) injection in combination with systemic perioperative IV antibiotic prophylaxis will reduce the rate of FRI one year after OEF fixation surgery.
Aim 2: Determine if local tobramycin injection has a negative effect on OEF union.
Aim 3: Compare bacterial speciation and antibiotic sensitivity among study patients who develop FRI between the control and treatment groups.

Study Design: This is a randomized clinical trial that will enroll 600 participants (300 in the control cohort, and 300 in the treatment cohort) over a three-year period at two Level I trauma centers, with the final year dedicated to data interpretation. The primary outcome will be presence or absence of FRI, while secondary outcomes will be nonunion status, bacterial speciation and antibiotic sensitivity in patients that develop FRI. The patients will be followed for one year to determine outcomes of interest.

15. SUBJECT TERMS

Open Extremity Fracture; Fracture Related Infection; Superficial Site Infection; Tobramycin; Antibiotic; Aminoglycoside; Injection; Nonunion; Bacterial Speciation; Prophylaxis

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	15	19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

TABLE OF CONTENTS

1. INTRODUCTION:

This study is a randomized clinical trial that tests the hypothesis that administering local tobramycin injection in combination with systemic perioperative intravenous (IV) antibiotic prophylaxis will reduce the rate of FRI one year after OEF fixation surgery. This study will also determine bacterial speciation and antibiotic sensitivity among study patients who develop FRI, as well as nonunion status among all participants.

Specific Aims:
Aim 1: Determine if a local dose of tobramycin (2 mg/mL) injection in combination with systemic perioperative IV antibiotic prophylaxis will reduce the rate of FRI one year after OEF fixation surgery.
Aim 2: Determine if local tobramycin injection has a negative effect on OEF union.
Aim 3: Compare bacterial speciation and antibiotic sensitivity among study patients who develop FRI between the control and treatment groups.

Study Design: This study will enroll 600 participants (300 in the control cohort, and 300 in the treatment cohort) over a three-year period at two Level I trauma centers. The primary outcome will be presence or absence of FRI, while secondary outcomes will be nonunion status, bacterial speciation and antibiotic sensitivity in patients that develop FRI. The patients will be followed for one year to determine outcomes of interest.

2. KEYWORDS:

Open Extremity Fracture; Fracture Related Infection; Superficial Site Infection; Tobramycin; Antibiotic; Aminoglycoside; Injection; Nonunion; Bacterial Speciation; Prophylaxis

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The Major Tasks of the project include:
Major Task 1: Acquire protocol approvals
- Milestone Achieved: Local IRB approval at UK and VUMC (11/8/2021; Continuing Review approved 3/17/2022)

Major Task 2: Prepare for data collection
- Milestone Achieved: Manual of Operations created (11/24/2021)
- Milestone Achieved: Research staff trained (11/23/2021)

Major Task 3: Participant recruitment and evaluation
- Milestone Achieved: 1st participant consented, screened, and enrolled (1/11/2022)
- Milestone to be Achieved: Last participant screened, consented, and enrolled
- Milestone to be Achieved: Last participant, last study visit

Major Task 4: Data analysis and dissemination of results
To date, we have enrolled 392/600 patients (65% enrollment completed) and completed 70% of specific objectives.

What was accomplished under these goals?

1. Accomplishments:

What were the major goals of the project?
Major Task 1: Acquire protocol approvals (Completed 100% of specific objectives)
Major Task 2: Prepare for data collection (Completed 100% of specific objectives)
Major Task 3: Participant recruitment, evaluation (65% enrollment completed; 392/600 patient enrolled to date, 70% of specific objectives completed.)
What was accomplished under these goals?
Major Task 1: Acquire protocol approvals
Regulatory Approvals
- Local IRB approval at the University of Kentucky (11/08/2021, IRB# 65241)
- HRPO approval (11/12/2021, HRPO Log numbers E02454.1a)
- Trial posted on clinicaltrials.gov (10/8/2021, NCT04964947)

Coordinate with sites for material transfer agreements or clinical trial agreements submission
- Original Timeline (Months 1-3)
- Status: Completed (11/15/2021)

Refine eligibility criteria, exclusion criteria, screening protocol
- Original Timeline (Months 1-3)
- Status: Completed (11/16/2021)

Finalize consent form & human subjects protocol
- Original Timeline (Months 1-3)
- Status: Completed (11/17/2021)

Coordinate with Sites for UK IRB review
- Original Timeline (Months 1-3)
- Status: Completed (11/05/2021)

Submit amendments, adverse events and protocol deviations as needed
- Original Timeline (As Needed)
- Status: Completed (11/16/2021)

Major Task 2: Prepare for data collection
Develop REDCap database to record subject information test data management, and quality control prior to enrolling patients
- Original Timeline (Months 1-3)
- Status: Completed (11/23/2021)

Finalize procedures for IDS drug preparation, concealment, and block randomization
- Original Timeline (Months 1-2)
- Status: Completed (11/29/2021)

Finalize procedures for surgeon injection training
- Original Timeline (Months 1-2)
- Status: Completed (11/17/2021)

Finalize surgeon training for data collection (infection, nonunion endpoint)
- Original Timeline (Months 1-3)
- Status: Completed (11/17/2021)

Finalize research team training (research coordinator and personnel) on study procedure and end point collection (bacterial speciation and antibiotic resistance)
- Original Timeline (Months 1-3)
- Status: Completed (11/23/2021)

Modify existing Manual of Operations with data collection methods and intervention specifics
- Original Timeline (Months 2-3)
- Status: Completed (11/24/2021)

Major Task 2: Prepare for data collection, continued
Milestone Achieved: Manual of Operations created
- Original Timeline (Month 3)
- Status: Completed (11/24/2021)

Site Initiation Visit with research and clinical staff (Monitor: Eben Carroll, MD)
- Original Timeline (Month 3)
- Status: Completed (11/29/2021)

Milestone Achieved: Research staff trained
- Original Timeline (Month 3)
- Status: Completed (11/23/2021)
  - Research coordinator (Matthew Kavolus, 11/22/2022)
  - Physician Sub-Investigators (Drs. Matuszewski, Moghadamian, Primm, Srinath training completed 11/17/2021)
- In the Statement of Work, we stated that the Site Initiation Visit would be completed by the study Monitor Dr. Eben Carroll. Due to the recent COVID-19 restrictions in place at our institute this meeting was conducted virtually with Drs. Arun Aneja (PI), Eben Carroll, Arnold Stromberg, Brooke Herdon, Cale Jacobs, Matthew Kavolus and William Obremskey on 11/29/2021.

Major Task 3: Participant recruitment, evaluation
Milestone Achieved: 1st participant consented, screened and enrolled
- Original Timeline (Month 4)
- Status: Completed (01/11/2022)

Continue subject recruitment (target accrual rate: 4 participants/week)
- Original Timeline (Months 4-36)
- Status: Incomplete/Ongoing

Follow patients for one year
- Original Timeline (Months 4-36)
- Status: Incomplete/Ongoing

Meetings with full research team
- Original Timeline (Quarterly)
- Status: Completed (05/16/2022, 09/15/2022, 12/15/2022, 03/14/2023, 06/22/2023)

Create DSMB report
- Original Timeline (Every 4 Months)
- Status: Incomplete

Clinical site monitoring (Eben Carroll)
- Original Timeline (Every 6 months)
- Status: Completed (3/18/2022, 11/01/2022, 06/14/2023)

Data quality audits
- Original Timeline (Every 6 months)
- Status: Completed (03/01/2022, 09/01/2022, 03/01/2023, 09/01/2023)

Coordinate with sites for annual IRB report for continuation review
- Original Timeline (Annually)
- Status: Completed (03/17/2022, 02/15/2023)

What opportunities for training and professional development has the project provided?

The project has allowed opportunities for training and professional development for our research staff at the University of Kentucky. Our four current research coordinators consist of three postdoctoral research fellows and one medical student currently taking a gap year to conduct research. All four researchers are aspiring orthopaedic surgeons who are interested in conducting research as part of their future practice. Participating in this study has allowed them to learn how to successfully design and implement a multi-site randomized controlled trial, how to collaborate with multiple stakeholders, and how to effectively budget a Department of Defense sponsored study. Additionally, these researchers also receive one-on-one mentorship from the PI regarding their pursuits in becoming orthopaedic surgeons, clinical and basic science research, work-life balance, and mental/physical wellness. These researchers have also served as mentors to medical students who have assisted us with this study. Our team has implemented a sustainable, team-oriented approach for pursuing our research endeavors, and this project is the embodiment of the hard work our team puts in on a daily basis.

How were the results disseminated to communities of interest?

Nothing to Report.

What do you plan to do during the next reporting period to accomplish the goals?

Enrollment: We will continue to have research staff onsite to screen 7 days per week at the participating hospitals. Screening is conducted through fracture conference each morning, daily communication with consulting providers, and the trauma census during the afternoons.
- Regulatory: We will complete our first DSMB report. We apologize for the delay in the completion of this report, as there has been confusion as to which party is responsible for this report.
- Continue clinical site monitoring with Karen Bowen/Dr. Eben Carroll
- Continue full team meetings: Virtual conferences with the entire research team at both sites.
- Continued training for Co-Investigator participation as needed.
- Continue to refine screening/recruiting methods to maximize enrollment.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What has been the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

We have had one change in approach/study design, which took place prior to the first participant being enrolled. This study was originally designed to have a "Tobramycin + Standard of Care" arm and a "Placebo + Standard of Care" arm. Due to surgeon hesitancy with injecting placebo (normal saline) and feasibility, the decision was made to modify the second arm (control group) to be "Standard of Care." This change was approved by the local IRBs at both UK and VUMC, as well as HRPO prior to it being implemented in the study design.

Actual or anticipated problems or delays and actions or plans to resolve them

In our previous Annual Report, we noted that our research team at UK had been working to resolve an issue with Pharmacy, Investigational Drug Services, and the OR nursing staff, where the study drug was not being properly documented as administered in patients' electronic medical record (EMR). After working with Investigational Drug Services, Pharmacy Billing, and the Clinical Research Support Office at UK, we were able to fully resolve this issue.

Changes that had a significant impact on expenditures

Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/ or select agents

Significant changes in use or care of human subjects

As previously mentioned, we have changed the control group from "Placebo + Standard of Care" to solely "Standard of Care." There was surgeon hesitancy with injecting placebo (normal saline) into a traumatic wound that may already be at risk of infection, edema, and increased compartment pressures. Due to these reasons, it was decided to do away with the placebo (normal saline) and have the control group be a simple Standard of Care group. This change was approved by both local IRBs at UK and VUMC, as well as HRPO prior to the first participant being enrolled. This change was made to better the care of human subjects and decrease the risks of injecting normal saline into a traumatic wound. Thus far, we have no significant deviations, unexpected outcomes, adverse events, or additional changes to report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**
  Journal publications.

Nothing to Report.

Books or other non-periodical, one-time publications.

Nothing to Report.

Other publications, conference papers and presentations.

Nothing to Report.

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Arun Aneja, MD PhD
Project Role: PI (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0002-1507-6863
Nearest person month worked: 24
Contribution to Project: Dr. Aneja has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, enrollment and screening procedures, and protocol manuscript preparation.

Name: William Obremskey, MD
Project Role: Co-PI (Vanderbilt University Medical Center)
Researcher Identifier (e.g. ORCID ID): 0000-0002-8942-1842
Nearest person month worked: 24
Contribution to Project: Dr. Obremskey has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, enrollment and screening procedures, and protocol manuscript preparation.

Name: Cale Jacobs, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0002-9300-5550
Nearest person month worked: 12
Contribution to Project: Dr. Jacobs has worked on all aspects of project including regulatory approvals, staff training, data collection procedures, and enrollment and screening procedures. Dr. Jacobs left the University of Kentucky at the end of September 2022, to serve as the Director of Outcomes Research at Mass General Brigham. He will no longer be serving as key personnel for this project.

Name: Brooke Herndon, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0003-1149-3683
Nearest person month worked: 24
Contribution to Project: Dr. Herndon is the clinical pharmacist for the project and has been involved with finalizing, randomization, drug administration, and enrollment procedures.

Name: Arnold Stromberg, PhD
Project Role: Co-I (University of Kentucky)
Researcher Identifier (e.g. ORCID ID): 0000-0003-0336-9789
Nearest person month worked: 24
Contribution to Project: Dr. Stromberg is the team's biostatistician and has been involved with the study design and implementing the randomization procedures and and assisted with protocol manuscript preparation. He will be involved throughout the project and will be responsible for all analyses performed at the conclusion of the trial.

Name: Eben Carroll, MD
Project Role: Monitor/Consultant (Atrium Health Wake Forest Baptist)
Researcher Identifier (e.g. ORCID ID): 0000-0001-8773-3319
Nearest person month worked: 24
Contribution to Project: Dr. Carroll has overseen all aspects of the project including regulatory approvals, staff training, data collection procedures, and enrollment and screening procedures during the initiation phase of the study.

Name: Matthew Kavolus, MD
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): 0000-0002-3712-1792
Nearest person month worked: 9
Contribution to Project: Dr. Kavolus was involved in finalizing data collection procedures, enrollment and screening procedures, and preparation of the protocol manuscript for OTA-I. He was directly involved with the day-to-day screening and enrolling process, assuring treatment administration, data collection and entry, patient follow up, troubleshooting, and organizing virtual conferences. Dr. Kavolus left the University of Kentucky at the end of May 2022 to begin his orthopaedic surgery residency in Atlanta, GA. He will no longer be serving as key personnel on this project.

Name: Austin Foster, MD
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): 0000-0003-3875-5401
Nearest person month worked: 16
Contribution to Project: Dr. Foster has been involved in finalizing data collection procedures, enrollment and screening procedures, and in preparation of the protocol manuscript for future submissions. He is and will be directly involved with the day-to-day screening and enrolling process, assuring treatment administration, data collection and entry, patient follow-up, troubleshooting, and organizing virtual conferences.

Name: Karen Trochez, M.L.A.S.
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 24
Contribution to Project: Karen Trochez has been involved in finalizing data collection procedures, and organizing all aspects at VUMC. She will be involved in enrollment and screening procedures and attends quarterly meetings. She is and will be directly involved with the day-to-day screening and enrolling process, assuring treatment administration, data collection and entry, patient follow up, troubleshooting, and organizing

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Vanderbilt University Medical Center (VUMC)
1215 21st Ave South
Nashville, TN 37232
PI: William Obremskey, MD (WO)
Partner's Contribution to Project: Collaboration, Partnering enrollment site

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: *A*