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TITLE: Novel Topical Antibiotic Therapy to Reduce Infection After Operative Treatment of Fractures at High Risk of Infection: TOBRA-A Multicenter RCT

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14. ABSTRACT

Background: Infection after treatment of high-energy military fractures is very common and continues to cause significant morbidity. Recently, a study showing the use of local vancomycin powder around metal hardware used to treat these at-risk fractures results in a reduced risk of infection. The powder is thought to create a kill zone around the metal, prevent bacterial colonization, and therefore reduce the rate of postoperative infection. **Specific Aims:** Our primary specific aim is to demonstrate that the infection rate (defined by CDC criteria) is lower in patients with at-risk fractures treated with standard of care as well as local vancomycin and tobramycin than patients treated with standard of care and vancomycin alone. Additional specific aims include investigation of the potential development of antibiotic resistance and examining bacterial sensitivities in patients who become infected in the treatment group and comparing the proportion of additional complications such as wound dehiscence and nonunion. **Study Design**: The proposed study is a multi-center prospective open label randomized controlled trial. The study will accumulate patients from 50 core civilian and 1 military center to ensure generalizability. The study group will be a a set of tibial plateau and pilon fractures previously shown to be at high risk of infection treated with plate and screw fixation. 1900 participants (950 per treatment arm) will be enrolled from METRC trauma centers over 24 months. Participants will be recruited during hospitalization for the initial injury. **Military Benefit and Clinical Impact**: Infection is a very common and serious complication associated with the treatment of high-energy military extremity trauma. Fixation of fractures in these injuries involves the use of metal implants. Plates and screws become colonized with bacteria and lead to high rates of infection that are not treated well with intravenous antibiotics. If the proposed study demonstrated the utility of this technology, it would have a dramatic effect on reducing the morbidity associated with extremity trauma. Further, a positive result could revolutionize the approach to prophylaxis against surgical site infection after orthopaedic fracture care in both the military and civilian arenas by moving the field toward technologies that focus on local antibiotics associated with the implanted devices. As of 9/30/21, 19 participants have been enrolled: 11 randomized to the control arm and 8 randomized to the treatment arm. There are two sites actively screening and other participating sites' status can be found in the attachment.

15. SUBJECT TERMS
Surgical site infection (SSI); vancomycin; tobramycin; topical antibiotics; tibial plateau; pilon; fracture fixation; orthopaedic surgery; trauma; METRC

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1. INTRODUCTION:

This study will build upon the success of the VANCO study (Contract Number: W81XWH-10-2-0134, FDA IND #119891) which enrolled 980 patients into a randomized controlled trial investigating topical Vancomycin powder versus no powder in patients having plate and screw fixation for fractures at risk of surgical site infection. The PI, Co-PI and most of the research team that led the VANCO study will serve similar roles in the current study. The proposed study design is a pragmatic, prospective, randomized controlled trial comparing deep surgical site infection rates in patients treated with either local Vancomycin powder or local Vancomycin and Tobramycin powders at the time of fracture fixation (in addition to standard of care). This study design will provide the highest quality evidence to investigate our hypothesis that the use of local Vancomycin and Tobramycin powders will be effective at decreasing deep surgical site infection in these at-risk patients. Participants (950 per treatment arm) will be enrolled from METRC trauma centers over a 24-month period and followed for 12 months following definitive fracture fixation surgery. Participants will be recruited during hospitalization for the initial injury.

2. KEYWORDS:

Surgical site infection (SSI); vancomycin; tobramycin; topical antibiotics; tibial plateau; pilon; fracture fixation; orthopaedic surgery; trauma; METRC

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The specific aims of the study are as follows:

- Specific Aim 1: Compare the proportion of deep surgical site infections (SSI) of the study injury within 365 days of definitive fracture fixation surgery in patients allocated to receive a combination of local Vancomycin and Tobramycin powders compared to patients allocated to local Vancomycin powder.
- Specific Aim 2: A series of sensitivity analyses will be conducted to look at alternative measures of deep SSI under Specific Aim 1. These sensitivity analyses will consider the following alternative endpoints of deep SSI: infection by gram-negative bacteria, infection by gram-positive bacteria, polymicrobial pathogenic infections, culture-negative infections, and cellulitis/skin infections.
- Specific Aim 3: To compare the safety of treatment with a combination of local Vancomycin and Tobramycin versus Vancomycin powder alone as measured by the proportion of antibiotic resistance in each arm.

The tasks and milestones set forth to meet the aims of the project, as stated in the approved scope of work, are shown in the table below. Items not yet completed and marked with an asterisk (*) in the status column below have additional information specifically addressed in other sections of this report.

Tasks and Milestones	Timeline	Status
Major Task 1: Study Initiation		
• Submission of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA)	Oct 2019-Nov 2019	Completed
• Refine eligibility criteria, exclusion criteria, screening protocol	Oct 2019-Nov 2019	Completed
• Finalize consent form & human subject protocol	Oct 2019-Nov 2019	Completed
• Develop case report forms (CRFs) for data capture, program, and pilot test REDCap	Oct 2019-Dec 2019	Completed
• Coordinate with Sites for IRB protocol submission	Oct 2019-Dec 2021	Started (90%)*
• Coordinate with Sites for IRB review	Oct 2019-Dec 2021	Started (50%)*
• Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	Oct 2019-Dec 2021	Started (30%)*
• *Milestone*: Local IRB approval at MCC and UMD	Mar 2021	Completed
• *Milestone*: HRPO approval for all protocols and local IRB approval through required participating sites	June 2021-Dec 2021	Started (30%)*
• *Milestone*: FDA IND Approval	Mar 2020	Completed
Major Task 2: Training Research Staff		
• Develop and conduct training for Research Coordinators on procedures for screening and consenting patients, study procedures, and data collection/reporting.	Feb 2020-May 2020	Completed
• Certify sites to begin screening and enrolling patients	May 2021-Sep 2021	Started*
• Conduct study initiation calls with each site to ensure procedures are in place	Feb 2020-June 2021	Started (80%)*
• *Milestone*: Research Staff Trained	June 2021	Started (70%)*
Major Task 3: Conduct Study		
• Clinical site Research Coordinators will screen and enroll eligible study patients	May 2021-April 2023	Started*
• Generate and distribute monthly enrollment and follow-up reports; provide ongoing training and support to address problems with enrollment as they are identified	October 2021-Mar 2023	
• Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	October 2021-July 2023	
• *Milestone*: The first patient enrolled at the principal investigator's site.	June 2021	Completed
• *Milestone*: All patients enrolled	Mar 2023	

• *Milestone*: All patient follow up complete	Mar 2024
Major Task 4: Outcome Adjudication	
• Develop data presentation profiles of cases ready for the adjudication	Jul 2022-Jan 2023
• Convene adjudication committee to determine study outcomes for records that have been fully completed.	Jan 2022-May 2024
• *Milestone*: Outcome Adjudication Completed	May 2024
Major Task 5: Data Analysis and Report Writing	
• Develop final analysis files	Jan 2024-Jul 2024
• Conduct analysis and write final reports and peer-reviewed publications	Mar 2024-Sep 2024
• Disseminate results published in peer-reviewed journals and presentation at professional and scientific meetings	Mar 2024-Sep 2024
• *Milestone*: Report findings from the final analysis	Sep 2024

What was accomplished under these goals?

As of September 30, 2021, 38 patients screened, and 19 participants have been enrolled: 11 randomized to the control arm and 8 randomized to the treatment arm. There was no protocol deviation. There was one adverse event reported at 2-week follow-up, the patient was readmitted due to leukocytosis. A medical monitor reviewed the patient's information and determined to be not related to the study and no further action is needed.

There are two sites actively screening and four additional sites with HRPO approval are waiting for certification to begin screening activity. In addition, two sites are waiting for HRPO approvals, and 5 sites are currently preparing for HRPO submission after receiving local IRB and sIRB approvals. We are continuing to work through the process of reliance agreements, local cede reviews and central IRB submission with other participating sites. Please refer to the attached appendix for the detailed list of the participating site status.

As the screening and enrollment has started, we have reviewed the summary data table shells that will be used as a part of the reporting system throughout the enrollment and follow-up period.

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

Nothing to report

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?

The next reporting period will be focused on gaining the necessary approvals to begin the full roll-out of the study to participating sites. Key activities will include:

1. FDA: We plan to submit an information amendment to the FDA addressing items that were not part of the clinical hold.
2. IRB: We will continue to add sites to Pearl IRB and develop reliance agreements.
3. Adjudication: Adjudication committee will begin reviewing new cases with enrolled patients.
4. Site management: Administrative tasks associated with securing site participation will continue.
5. Screening and enrollment: Sites will begin screening and enrollment once they are certified.
6. Data quality checks: Data quality checks, including site data queries, will be programmed and implemented. Also, weekly screening, enrollment, and follow-up reports will be developed.
7. Monthly check-in meetings: Once the sites begin screening and enrollment, the coordinating center will conduct monthly check-in calls to address any questions as the sites are implementing the study.

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 was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

The new requirement for a single IRB has led to some delays. Because the use of a sIRB is fairly new to most of our participating sites, it is slowing down the both local and central IRB submission processes. We are providing extra time and effort for additional meetings and communications to follow-up on individual sites' sIRB policy and submission process when compared with other studies that do not require a sIRB.

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

The most likely anticipated challenges are associated with coronavirus pandemic. We continue to maintain regular communications with Pearl IRB (the expected IRB of record) as well as with clinical sites and investigators during this time.

As mentioned in the previous section, finalizing contracts with additional sites and walking each site through local IRB and central IRB submission process will be much more extensive process than we have planned.

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

Nothing 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: Project Role: ORCID ID: Effort: Contribution:	Robert O'Toole Principal Investigator 0000-0002-5628-6584 10% Dr. O'Toole led the overall project effort and has overseen the development of the study protocol and submission of the IND application to the FDA.
Name: Project Role: ORCID ID: Effort: Contribution:	Manjari Joshi Co-Investigator Not available 5% Dr. Joshi has provided oversight and expertise on all project matters related to infectious disease.
Name: Project Role: ORCID ID: Effort: Contribution:	Nathan O'Hara Co-Investigator 0000-0003-0537-3474 15% Mr. O'Hara has managed all administrative aspects of the project at the lead institution and contributed to the development of the protocol.
Name: Project Role: ORCID ID: Effort: Contribution:	Renan Castillo MCC Principal Investigator 0000-0003-0473-5891 0.60 Dr. Castillo contributed to the development of protocol and statistical planning as well as led all project efforts at the METRC Coordinating Center.
Name: Project Role: ORCID ID: Effort: Contribution:	Anthony Carlini MCC Co-Investigator 0000-0003-1419-4515 0.60 Mr. Carlini has organized all project efforts across institutions and has developed/drafted study documents and reports.
Name: Project Role: ORCID ID: Effort: Contribution:	Suna Chung MCC Project Director Not Available 1.80 Ms. Chung has organized all project efforts across institutions and has developed/drafted study documents and reports.
Name: Project Role: ORCID ID: Effort:	Richard Thompson Biostatistician 0000-0001-8378-4426 0.60

Contribution:	Dr. Thompson has oversight and expertise on all project matters related to statistical planning.
Name: Project Role: ORCID ID: Effort: Contribution:	Susan Collins Study Manager Not Available 2.40 Ms. Collins corresponded with participating centers, organized site survey responses, and drafted the consent documents and case report forms.
Name: Project Role: ORCID ID: Effort: Contribution:	Elias Weston-Farber Programmer Not Available 0.60 Mr. Weston-Farber supports the analysis of the data under the supervision of the study investigators.
Name: Project Role: ORCID ID: Effort: Contribution:	Paige Sullivan Programmer Not Available 0.60 Ms. Sullivan supports programming of the REDCap database under the supervision of the study investigators.
Name: Project Role: ORCID ID: Effort: Contribution:	Jack Dagg Data Analyst Not Available 1.80 Mr. Dagg supports the analysis of the data under the supervision of the study investigators.
Name: Project Role: ORCID ID: Effort: Contribution:	Christopher Pierce Research Assistant Not Available 0.30 Mr. Pierce supports the analysis of the data under the supervision of the study investigators.
Name: Project Role: ORCID ID: Effort: Contribution:	Chris Witczak Financial Analyst Not Available 0.24 Mr. Witczak set up the study account and prepared subaward paperwork for participating centers.

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

Mr. Christopher Pierce has joined METRC team as a research assistant.

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

An updated Quad Chart is included as Attachment 1.

9. APPENDICES: