AWARD NUMBER: W81XWH-19-1-0848

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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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: Infection after treatment of high energy military fractures is very common and continues to cause significant morbidity. Recently, a study showing 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. This study seeks to expand upon the findings of this previous work and expand the potential antibiotic coverage by adding local tobramycin powder to the treatment regimen.
Objective/Hypothesis: Treatment of patients with new technique aimed at delivering both Vancomycin and Tobramycin antibiotics locally in addition to standard of care treatment will reduce infection compared to patients who are only treated with standard of care and local Vancomycin.
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 blinded randomized controlled trial. The study will use the DOD funded Major Extremity Research Consortium to accumulate patients from 50 core civilian and 1 military center to insure the highest quality of data collection, analysis, and scientific integrity. The study group will be high energy tibial plateau and pilon fractures treated with plate and screw fixation in a staged fashion as this patient population has been shown to have a high infection rate and is amenable to the existing technology. 1900 participants (950 per treatment arm) will be enrolled from METRC trauma centers over a 24-month period. 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 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 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.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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:** *Provide a brief list of keywords (limit to 20 words).*

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

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The specific aims of the study are as follows:

- Specific Aim 1: Compare the proportion of deep surgical site infections within 6 months in patients treated with local Vancomycin powder compared to those treated with a combination of local Vancomycin and Tobramycin powders.
- Specific Aim 2: Compare the proportion of infections involving gram-negative bacteria in patients treated with a combination of local Vancomycin and Tobramycin to patients treated with local Vancomycin powder alone.
- Specific Aim 3: Compare the proportion of superficial surgical site infections, wound dehiscence, and nonunion in patients treated with a combination of local Vancomycin and Tobramycin to patients treated with local Vancomycin powder alone.
- Specific Aim 4: Among patients who develop deep surgical site infections, compare antibiotic sensitivities of the bacteria in patients treated with a combination of local Vancomycin and Tobramycin to patients treated with local Vancomycin powder alone.

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 subjects 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 2019	Started (80%)*
• Coordinate with Sites for IRB review	Oct 2019-Mar 2020	Started (70%)*
• Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	Oct 2019-Mar 2020	
• *Milestone*: Local IRB approval at MCC and UMD	Mar 2020	
• *Milestone*: HRPO approval for all protocols and local IRB approval through TBD	Mar 2020	
• *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	Started (30%)*
• Certify sites to begin screening and enrolling patients	Feb 2020-May 2020	
• Conduct study initiation calls with each site to ensure procedures are in place	Feb 2020-May 2020	
• *Milestone*: Research Staff Trained	May 2020	
Major Task 3: Conduct Study		
• Clinical site Research Coordinators will screen and enroll eligible study patients	Mar 2020-Mar 2022	

• Generate and distribute monthly enrollment and follow-up reports; provide ongoing training and support to address problems with enrollment as they are identified	Jun 2020-Mar 2022
• Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	Sep 2020-July 2023
• *Milestone*: First patient enrolled at principal investigator's site.	Mar 2020
• *Milestone*: All patients enrolled	Mar 2022
• *Milestone*: All patient follow up complete	Mar 2023
Major Task 4: Outcome Adjudication	
• Develop data presentation profiles of cases for ready for adjudication	Jul 2022-Jan 2023
• Convene adjudication committee to determine study outcomes for records that have been fully completed.	Jan 2023-May 2023
• *Milestone*: Outcome Adjudication Completed	May 2023
Major Task 5: Data Analysis and Report Writing	
• Develop final analysis files	Jan 2023-Jul 2023
• Conduct analysis and write final reports and peer-reviewed publications	Mar 2023-Sep 2023
• Disseminate results publication in peer reviewed journals and presentation at professional and scientific meetings	Mar 2023-Sep 2023
• *Milestone*: Report findings from final analysis	Sep 2023

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting

The majority of activities for this reporting period continued to center around project planning and study initiation.

Since the protocol committee's initial review of the FDA-approved protocol, the study team has worked to implement the suggestions provided. This effort included a review of the eligible study injuries and clarification of multiple outcome definitions. A brief survey of laboratory and tissue culturing procedures was completed has led to revisions in data collection requirements based on the results. The statistical analysis plan (SAP) and study outcome adjudication procedures were finalized during this reporting period. In previous studies (VANCO) this work was not finished until years into study enrollment, but we wished to do this earlier to improve quality of the data and analysis process. Case report forms (CRFs) and REDCap database have been developed and pilot tested.

Significant work was required stemming from the new requirement since the grant was originally submitted that we have a centralized IRB. Our original sIRB was Advarra but they have subsequently increased prices significantly and presenting a real study threat financially. A search for a new sIRB was performed and we chose Pearl. The contract with Pearl IRB for sIRB application submission is currently being finalized. In addition, administrative tasks, such as contracting with participating sites continued during this reporting period. Site training materials and certification documents have been developed.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

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: The master protocol will be submitted to the central IRB early in the upcoming reporting period. The METRC Coordinating Center will work with participating sites to identify the "local site context" issues that should be addressed.
3. Adjudication: We will finalize our initial work to create and test the study outcome adjudication system, including providing panel members with an opportunity to work with test cases before study initiation.
4. Training: Materials for the initial investigator and coordinator training will be finalized.
5. Site management: Administrative tasks associated with securing site participation will continue.
6. We will enroll our first patient at the PI's site.
7. Screening and enrollment: Sites will begin screening and enrollment once they are certified through the training process.
8. Data quality checks: We plan to create data quality check tools including queries. Also,

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and

research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Our initial timeline was very aggressive, and we hoped to enroll our first patients in 6 months based on our previous experience with the VANCO trial. However, two events occurred that caused delay: the COVID-19 pandemic and the issues with the sIRB as mentioned above. It looks that this first patient enrollment will be in the first quarter of year 2 which is reasonable based on prior successful METRC studies.

We have attempted to minimize the work delays associated with the COVID-19 pandemic and have continued to work remotely. METRC is enrolling in many studies at high levels again so we hope that this will not add further delays, but it is of course possible based on the course of the pandemic in the coming year.

As mentioned above the new requirement for a single IRB has led to some delays. The budget had to be reworked to find a way to pay for this sIRB. Further, Advarra has raised their prices substantially making them too expensive to use for this study. We had search and evaluate other sIRB options and are underway with Pearl currently. This process added 3-6 months of delay to the project.

The study team will continue to adjust plans as needed based on the pandemic, but we intend to launch the study in the period that follows. We anticipate sIRB approval in the coming weeks. Upon the sIRB approval, site training and certification will be provided to the participating sites to begin screening and enrollment.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period 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.

Of note, there have been some instances of tobramycin shortages nationally that are likely related to production issues and the COVID-19 pandemic. We have been following this closely and anticipate this should be resolved soon but of course a national tobramycin shortage would delay the study if it occurs.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report

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

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to Report

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to Report

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to Report

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to Report

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention,

diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name: Robert O'Toole
Project Role: Principal Investigator
ORCID ID: 0000-0002-5628-6584
Effort: 10%
Contribution: 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: Manjari Joshi
Project Role: Co-Investigator

Name: Richard Thompson
Project Role: Biostatistician
ORCID ID: 0000-0001-8378-4426
Effort: 1.20
Contribution: Dr. Thompson has oversight and expertise on all project matters related to statistical planning

Name: Anthony Carlini
Project Role: Project Director
ORCID ID: 0000-0003-1419-4515
Effort: 0.60
Contribution: Mr. Carlini has organized all project efforts across institutions and has developed/drafted study documents and reports. Effort is being reduced to 5% for current project year.

Name: Suna Chung
Project Role: Project Director
ORCID ID: N/A
Effort: 1.05
Contribution: Ms. Chung is supporting Mr. Carlini in organizing all project efforts across institutions and has developed/drafted study documents and reports. New project director effective March 2020.

Name: Elias Weston-Farber
Project Role: Programmer

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Suna Chung (Project Director): New Project Director effective March 2020
Jack Dagg (Data Analyst): New Data Analyst effective March 2020

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

An updated Quad Chart is included as Attachment 1.

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*