AWARD NUMBER:	W81XWH-21-2-0026
TITLE:	Prophylactic Antibiotic-Coated Nail to Prevent Infection: A Clinical Triall
PRINCIPAL INVESTIGATOR:	Joseph R. Hsu, MD
CONTRACTING ORGANIZATION:	Atrium Health
REPORT DATE:	October 2022
TYPE OF REPORT:	Annual Progress Report
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 2022	Annual Progress Report	30SEPT2021 – 29SEPT2022

4. TITLE AND SUBTITLE
Prophylactic Antibiotic-Coated Nail to Prevent Infection: A Clinical Trial

5a. CONTRACT NUMBER
W81XWH-21-2-0026

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

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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 is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Open tibia fractures are severe and common injuries sustained by Wounded Warriors in combat. Osteomyelitis and deep infection are unfortunately common after severe open fractures. Rates of infection following high-energy open fractures range from 6-40%. Furthermore, the injury mechanisms associated with the military involving penetrating fragments contribute to a higher rate of infection as compared to the civilian sector, in which blunt trauma is more common. To date, the field of orthopaedic surgery has not experienced a significant reduction in infection rates, despite numerous studies of a variety of different treatment options. Therefore, any novel strategy to reduce infection warrants rigorous study. The goal of this study is to investigate a potential treatment for serious open tibia fractures which are likely to become infected.

Usually, these injuries are treated with a nail without antibiotic coating. The other treatment option is to use an antibiotic-coated nail (vancomycin, tobramycin & gentamicin). Antibiotic coated nails are commonly used for patients who have an infection. Using an antibiotic coated nail for prevention would be an extension of this practice. This study will compare infection rates among patients treated with an antibiotic coated nail and people treated with a standard of care nail (nail without antibiotic coating).

The study addresses the FY20 PRORP CTA Focus Area of fracture-related infection, specifically prevention of infection. The study will include patients with severe open tibia fractures because these injuries are at very high risk of infection. By preventing infection in these patients, we can avoid readmissions, reoperations, and extended antibiotic regimens. In addition, a reduction in infection rate will mean patients will be able to return to work or duty and have lower rates of disability.

This intervention offers the possibility of decreasing infection with its subsequent negative health impact, resource utilization, and loss to duty with a low cost intervention that can be performed anywhere in the military that is equiped for definitive fracture care.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRDC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			**19b. TELEPHONE NUMBER** *(include area code)*
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Prescribed by ANSI Std. Z39.18

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

This study addresses the focus area of fracture-related infections, specifically prevention of infection. This is a randomized clinical trial to compare two treatments for patients (n=484) with severe open tibia fractures: 1) primary treatment with prophylactic antibiotic-coated intramedullary nail (1CN) and 2) traditional standard of care intramedullary nail (SN). The primary outcome is deep surgical site infection. Secondary outcomes include adverse events, nail delamination, return to operating room, rate of union, return to duty/work, and cost.

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

Infection; fracture; antibiotic-coated nail; trauma; prevention

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.

Specific Aim 1: To conduct a randomized clinical trial to compare infection rates among patients treated primarily with a prophylactic antibiotic coated nail to prevent infection and patients treated with standard of care nail.

Primary Hypothesis: Utilizing a prophylactic antibiotic-coated IM nail during the definitive fixation procedure will reduce infection rates for patients with severe lower-extremity fractures as compared to a standard of care nail.

Secondary Hypothesis: Patients treated primarily with a prophylactic antibiotic-coated IM nail will have similar rates of adverse events and nonunions as patients treated with a standard of care nail.

Specific Aim 2: To determine cost effectiveness of this novel intervention to target primary prevention of deep infection.

Hypothesis 2.1: Patients treated primarily with a prophylactic antibiotic-coated IM nail to prevent infection will have higher initial costs than those treated with a standard of care nail. Lower infection rates in the treatment group will result in net lower costs by avoiding, which will be negated by a lower infection rate resulting in readmission, reoperation, and extended antibiotic regimen.

Hypothesis 2.2: Patients treated primarily with a prophylactic antibiotic-coated IM nail will have higher rates of Return to Duty/Work and decreased disability compared to those in the standard of care group due to lower rates of infection.

	Proposed Timeline	**Status**
Major Task 1: Study Initiation	Months	
Subtask 1: Finalize protocol	1-3	Complete
Subtask 2: Develop case report forms (CRF) for data capture.	1-3	Complete
Subtask 3: Program and pilot data capture using REDCap.	1-3	Complete

Subtask 4: Obtain initial IRB approval via the single IRB.	1-3	In progress (submitted and under review)
Subtask 5: Obtain FDA Approval.	2-4	Complete
Subtask 6: Distribute approved protocol and obtain IRB approval for all participating sites via the single IRB	5	Pending initial IRB approval
Subtask 7: USAMRMC Human Research Protections Office review and approval	3-6	In progress
Milestone Achieved: IRB approval for all sites via single IRB	7	
Milestone Achieved: HRPO approval for all site protocols	7	
Subtask 8: Certify sites to begin screening and enrolling patients, and conduct initiation calls	7-8	In progress
Milestone Achieved: Research staff trained and study initiated	9	
Major Task 2: Enroll and Follow Patients in Clinical Trial		
Subtask 1: Screen and enroll eligible patients	8-29	Pending IRB approval
Subtask 2: Follow all enrolled patients for 12 months	20-41	
Subtask 4: Generate and distribute monthly enrollment and follow-up reports to manage study progress. Provide on-going training and support to address problems with enrollment and follow-up as they are identified.	11-42	Pending IRB approval and initiation of study
Subtask 5: Generate and distribute data quality reports to monitor data completeness, check for errors and inconsistencies.	11-42	Pending IRB approval and initiation of study
Milestone Achieved: Patients enrolled and followed for 12 months	41	
Major Task 3: Data Analysis		
Subtask 1: Develop final data files and conduct analysis.	41-46	
Subtask 2: Write final report and peer-reviewed publications	46-48	
Milestone Achieved: Data analyzed and results submitted for publication	48	

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 activities to reporting accomplishments.

Major activities planned for Year 1 are highlighted in the timeline above. During this reporting period, we obtained FDA approval (IND 160552, 9/7/2022). We submitted the protocol to the single IRB on 09/16/2022. We have begun coordinating with sites to complete subawards. Following initial IRB approval, we will submit to DOD HRPO. Upon DOD HRPO approval, we will begin enrolling patients at the Atrium Health hospitals covered by that IRB (AH Carolinas Medical Center, AH Cabarrus, and AH Wake Forest Baptist), with a target of beginning enrollment before the end of 2022. Then, we will distribute the protocol to all sites with subawards to obtain IRB approval. Upon execution of subawards and IRB approval at each site, we will train sites and begin enrollment.

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.

During the next reporting cycle, we aim to complete IRB and HRPO submissions so we can begin to certify sites to begin enrollment. We aim to begin enrollment at the lead site once we have approval from HRPO.

***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:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

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.

We experienced delay due to multiple rounds of edits to the IND for the FDA, but received approval in September. We have not encountered any other problems or delays. Due to our delay getting FDA approval, we will now be delayed beginning enrollment. This may pose a threat to obtaining the number of patients required during the study period. We will attempt to recruit additional sites if enrollment is slow.

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 or care of vertebrate animals

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

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".

Name: Project Role: Research Identifier: Effort: Contribution:	Joseph Hsu, MD Principal Investigator 0000-0001-9341-2554 0.60 CM Oversees all aspects of the study.
Name: Project Role: Research Identifier: Effort: Contribution:	Rachel Seymour, PhD Co-Principal Investigator 0000-0002-9203-8297 0.60 CM Oversees scientific management and management of the coordinating center, including regulatory, development of CRFs and site engagement and training.
Name: Project Role: Research Identifier: Effort: Contribution:	Meghan Wally, PhD Co-Investigator 0000-0003-4540-532X 1.20 CM Manages overall study timeline and collaborates with PI and Co-PI on implementation of the study.
Name: Project Role: Research Identifier: Effort: Contribution:	Susan Odum Co-investigator/Statistician 0000-0001-7769-4782 0.60 CM Responsible for developing and implementing the analysis plan; work during this first year has focused on ensuring that the data capture plan will match the analysis plan.
Name: Project Role: Research Identifier: Effort: Contribution:	Christine Churchill Project manager NA 2.40 CM Manages communication with the sites, development and implementation of the screening and enrollment plan and the data capture system, site training and regulatory requirements.
Name: Project Role: Research Identifier: Effort:	Erica Grochowski Research Coordinator NA 0.60 CM

Contribution:	Supports all regulatory activities including human subjects and FDA.
Name: Project Role: Research Identifier: Effort: Contribution:	Tamar Roomian Statistician NA 0.50 CM Supports Dr. Odum, statistician, in development and implementation of the analysis plan.
Name: Project Role: Research Identifier: Effort: Contribution:	Meera Sumith Data Management Coordinator NA 2.40 CM Database development and testing, implementation of the data quality management system, including development of communication with sites regarding data quality.

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.

Nothing to report.

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*

- *Other*.

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://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

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

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.*