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TITLE: Prophylactic Antibiotic-Coated Nail to Prevent Infection: A Clinical Trial

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6. AUTHOR(S)
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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 equipped 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**
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1. INTRODUCTION:

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:

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

3. ACCOMPLISHMENTS:

What were the major goals of the project?

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	Complete

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	Complete
Subtask 7: USAMRMC Human Research Protections Office review and approval	3-6	Complete
Milestone Achieved: IRB approval for all sites via single IRB	7	In progress
Milestone Achieved: HRPO approval for all site protocols	7	In progress
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	In progress
Major Task 2: Enroll and Follow Patients in Clinical Trial		
Subtask 1: Screen and enroll eligible patients	8-29	In progress
Subtask 2: Follow all enrolled patients for 12 months	20-41	In progress
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	In progress
Subtask 5: Generate and distribute data quality reports to monitor data completeness, check for errors and inconsistencies.	11-42	In progress
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?

Major activities planned for Year 2 are highlighted in the timeline above. During this reporting period, we began screening and enrollment at AH Carolinas Medical Center and AH Cabarrus, and have screened 70 patients and enrolled 10. We conducted training at UNC Chapel Hill, and they will begin screening and enrollment soon. We continue to engage with sites to complete all subawards, and we have distributed the protocol to all the sites to begin obtaining local IRB approval. Upon execution of subawards and IRB approval at each additional site, we will train those sites to begin enrollment.

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?

During the next reporting cycle, we aim to finalize subawards with additional sites and continue screening and enrollment, as well as data monitoring at all sites.

***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:

Changes in approach and reasons for change

Nothing to report.

Actual or anticipated problems or delays 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

Nothing to report.

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

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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:

- **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: Research Identifier: Effort: Contribution:	Joseph Hsu, MD Principal Investigator 0000-0001-9341-2554 0.12 CM Oversees all aspects of the study.
Name: Project Role: Research Identifier: Effort: Contribution:	Rachel Seymour, PhD Co-Principal Investigator 0000-0002-9203-8297 0.33 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 0.75 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 0.24 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: Contribution:	Erica Grochowski Research Coordinator NA 0.24 CM Supports all regulatory activities including human subjects and FDA.

Name:	Meera Sumith
Project Role:	Data Management Coordinator
Research Identifier:	NA
Effort:	2.40 CM
Contribution:	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?

Drs. Hsu, Seymour, Wally & Odum have updates to their active other support. The projects listed below are now active.

Dr. Hsu

- Primary Subtalar Arthrodesis for Calcaneal Fractures to Optimize Performance: A Randomized Clinical Trial (1.2 CM)
- Identifying and Treating Depression in the Orthopaedic Trauma Population (0 CM)
- Single Implant Versus Dual Implant Fixation of Distal Femur Extra Articular and Complete Articular Fractures (0.24 CM)

Dr. Rachel Seymour

- Primary Subtalar Arthrodesis for Calcaneal Fractures to Optimize Performance: A Randomized Clinical Trial (1.8 CM)
- A Randomized, Multi-Center, Double-Blind, Parallel Study to Examine the Effect of Lipogems Processed Microfragmented Adipose Tissue in Comparison to Corticosteroid for the Treatment of Knee Osteoarthritis (1.44 CM Y1, 1.2 CM Y2, 0.6 CM Y3)
- Single Implant Versus Dual Implant Fixation of Distal Femur Extra Articular and Complete Articular Fractures (1.8 CM)

Dr. Meghan Wally

- Primary Subtalar Arthrodesis for Calcaneal Fractures to Optimize Performance: A Randomized Clinical Trial (1.8 CM)
- Identifying and Treating Depression in the Orthopaedic Trauma Population
- APP Study (0.2 CM)
- Single Implant Versus Dual Implant Fixation of Distal Femur Extra Articular and Complete Articular Fractures (0.6 CM)

Dr. Susan Odum

- Primary Subtalar Arthrodesis for Calcaneal Fractures to Optimize Performance: A Randomized Clinical Trial (0.6 CM)
- Does Medial Collateral Ligament and Posterior Oblique Ligament Repair with Internal Bracing Restore Native Joint Stability Under Cyclic Loading: An In Vitro Biomechanical Study (0.24 CM)
- Single Implant Versus Dual Implant Fixation of Distal Femur Extra Articular and Complete Articular Fractures (0.6 CM)
- Single-Bundle Fibular-Based Posterolateral Corner Reconstruction with InternalBrace Augmentation: Biomechanical Comparisons to Intact Ligamentous State and Reconstruction Without InternalBrace Augmentation (0.24 CM)

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES: *N/A*