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TITLE: SEXTANT: Evaluation of a New Strategy for Protocolized Antibiotic Care for Severe Open Fractures

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Background. Infection remains the most common and significant complication following high-energy open fractures, with rates ranging from 15-40%. Up to 15% of recent combat casualties develop osteomyelitis. At present, antibiotics are delivered in an empiric fashion, as the surgeon does not know the bacterial profile of the open fracture wound at the time of injury or at the time of wound coverage/closure. Building on conclusions from a prospective observational study that evaluated the bioburden of severe lower extremity wounds sampled at the time of final wound coverage or closure, this project will study the impact of a new antibiotic delivery treatment strategy compared to the existing standard of care antibiotic prophylaxis strategy to evaluate the impact on deep SSI. **Objective**. The overall objective of the proposed study is to perform a PRCT in order to compare the antibiotic and infection related outcomes of a new antibiotic strategy for use in the care of severe open extremity fractures to the current standard of care. **Study Design**. This study will be conducted in 30 established METRC level 1 trauma centers. The patients will be randomized as close to admission as possible to either 1) Standard of Care (SOC) prophylactic open fracture protocol or 2) experimental protocol (SEXTANT) that will direct a wound bioburden targeted systemic and topical vancomycin powder and tobramycin powder antibiotic treatment at the time of final wound closure/coverage. The study will compare results of the current SOC prophylactic coverage to the SEXTANT protocol. As of 9/30/21, 2 participants have been enrolled in the study; 1 randomized in control and 1 randomized in treatment arm. There are three sites actively screening and other participating sites status can be found in the attachment.

15. SUBJECT TERMS
Orthopaedic trauma; surgical site infection; local antibiotics

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1. INTRODUCTION:

Background. Infection remains the most common and significant complication following high-energy open fractures, with rates ranging from 15-40%1-8. Up to 15% of recent combat casualties develop osteomyelitis.2,4,9,10 At present, antibiotics are delivered in an empiric fashion, as the surgeon does not know the bacterial profile of the open fracture wound at the time of injury or at the time of wound coverage/closure. Building on conclusions from a prospective observational study that evaluated the bioburden of severe lower extremity wounds sampled at the time of final wound coverage or closure, this project will study the impact of a new antibiotic delivery *treatment strategy* compared to the existing standard of care antibiotic *prophylaxis strategy* to evaluate the impact on deep SSI.
Objective. The overall objective of the proposed study is to perform a PRCT in order to compare the antibiotic and infection related outcomes of a new antibiotic strategy for use in the care of severe open extremity fractures to the current standard of care.

2. KEYWORDS:

Orthopaedic trauma; surgical site infection; local antibiotics

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The specific aims of the study are as follows:

- Specific Aim 1: To compare the infection rates of the current severe open fracture prophylactic antibiotic strategy to a revised SEXTANT treatment strategy designed to address the modern wound bioburden at the time of wound closure.
- Specific Aim 2: To compare the terminal bioburden of the wounds at the time of definitive closure / coverage as sampled by standard tissue microbiology.
- Specific Aim 3: To compare rates of antibiotic-related serious adverse events (SAEs) of the two treatment groups.
- Exploratory Aim 4: To pilot the use of available and emerging rapid PCR platforms for wound pathogen identification in a sub-cohort of patients.

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.

	Timeline	Status
Major Task 1: Study Initiation	Months	
Refine eligibility criteria, exclusion criteria, screening protocol	1-6	Completed
Finalize consent form & human subjects protocol	1-6	Completed
Develop case report forms (CRFs) for data capture, program and pilot test REDCap	1-6	Completed
Coordinate with Sites for IRB protocol submission	15-20	Started (80%)*
Coordinate with Sites for Advarra IRB review	15-20	Started (60%)*
Coordinate with Sites for Military 2nd level IRB review (ORP/HRPO)	15-20	Started (20%)*
Submit amendments, adverse events and protocol deviations as needed	As Needed	
Coordinate with Sites for annual IRB report for continuing review	Annually	
Milestone Achieved: Local IRB approval and Advarra	20	
Milestone Achieved: HRPO approval for all protocols	20	
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.	6-8	Completed
Certify sites to begin screening and enrolling patients	15-20	Started*
Conduct study initiation calls with each site to ensure procedures are in place	15-20	Started*
Milestone Achieved: Research Staff Trained	20	
Major Task 3: Microbiology and PCR Processing		
Establish agreement with central laboratory to process tissue samples and provide microbiology culture results	1	Completed
Establish agreement with central laboratory to perform “real time” PCR sequencing for a subset of cases associated with Exploratory Aim #4	1	Completed
Develop sampling framework to identify the appropriate cases for Exploratory Aim #4.	1	Completed
Establish site procedures for appropriate tissue sampling, storage and shipping.	6	Completed
Tissue samples collected and sent to appropriate laboratories	15-40	
Milestone Achieved: PCR Results Available for Subset of Cases (Exploratory Aim #4)	39	
Milestone Achieved: Culture Results Available for All Tissue Samples	40	
Major Task 4: Conduct Study		
Clinical site Research Coordinators will screen and enroll eligible study patients	15-40	Started*
Generate and distribute monthly enrollment and follow-up reports; provide ongoing training and support to address problems with enrollment as they are identified	15-46	

Generate and distribute data quality reports to monitor data completeness; check for errors and inconsistencies	15-46
Milestone Achieved: All patients enrolled	40
Milestone Achieved: All patient follow up complete	52
Major Task 5: Data Analysis and Report Writing	
Develop final analysis files	40-46
Conduct analysis and write final reports and peer-reviewed publications	52-60
Disseminate results publication in peer reviewed journals and presentation at professional and scientific meetings	52-60
Milestone Achieved: Report findings from final analysis	60

What was accomplished under these goals?

As of September 30, 2021, 4 patients screened, and 2 participants have been enrolled: 1 randomized to the control arm and 1 randomized to the treatment arm. There was no protocol deviation and adverse event reported.

There are three sites actively screening and three additional sites with HRPO approval are waiting for certification to begin screening activity. In addition, two 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.

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. Statistical Analysis Plan (SAP) also has been developed and is currently in the process of finalization.

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 Advarra 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.
8. Bioburden data: We will begin reviewing Bioburden data and develop SOP.
9. Infection Disease (ID) Steering Committee: ID steering committee will hold meetings and communicate via emails to review and address questions on participating site's antibiotic protocol and develop a master version of the antibiotic protocol for 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:

Changes in approach and reasons for change

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 the unknown trajectory of the coronavirus pandemic over the coming months. We continue to maintain regular communications with Advarra IRB (the 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**

  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?

Personnel	Role	Effort
Michael Bosse	PI	0.51 CM
Rachel Seymour	Co-I	0.60 CM

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:	Richard Thompson Biostatistician 0000-0001-8378-4426 0.60 Dr. Thompson has oversight and expertise on all project matters related to statistical planning.

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: Contribution:	Susan Collins MCC 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 the 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:	Chris Witczak Financial Analyst Not Available 0.24 Mr. Witczak set up the study account and prepared subaward paperwork for participating centers.
Name:	Christopher Pierce

Project Role:	Research Assistant
ORCID ID:	Not Available
Effort:	0.30
Contribution:	Mr. Pierce supports the analysis of the data under the supervision of the study investigators.

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 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:

Site name	HRPO assigned #	Target required for clinical significance	Local IRB submission status	Submitted/ approved by Advarra sIRB	Submitted/ approved by DoD HRPO	# of subjects screened/original planned target	# of patients enrolled/original planned target
Carolinas Medical Center	E00881.1b	96	N/A	Submitted 12/8/20 Approved 12/15/20	Submitted 2/24/21 Approved 3/8/21	4/96	2/96
Hennepin County Medical Center	E00881.1c	16	Approved	Submitted 6/8/21 Approved 7/2/21	Submitted 7/6/21 Approved 7/28/21	0/16	0/16
University of Mississippi Medical Center	E00881.1d	16	Approved	Submitted 6/8/21 Approved 6/23/21	Submitted 7/16/21 Approved 7/28/21	0/16	0/16
Ohio State University	E00881.1e	16	Approved	Submitted 7/27/21 Approved 8/4/21	Submitted 9/13/21 Approved 9/22/21		
Methodist Hospital, Indiana University	E00881.1f	16	Approved	Submitted 8/5/21 Approved 8/20/21	Submitted 9/13/21 Approved 9/23/21		
McGovern Medical School at UTHealth Houston	E00881.1g	16	Approved	Submitted 8/4/21 Approved 8/17/21	Submitted 9/14/21 Approved 9/28/21		
Dartmouth Hitchcock Clinic	E00881.1h	16	Approved	Submitted 7/30/21 Approved 9/7/21	Submitted 10/5/21		
MetroHealth Medical Center	E00881.1i	16	Approved	Submitted 8/24/21 Approved 9/5/21	Submitted 10/6/21		
University of California at San Francisco	Not assigned yet	16	Approved	Submitted 8/16/21 Approved 8/23/21	Pending		
Allegheny General Hospital	Not assigned yet	16	Approved	Submitted	Not available yet		

Site name	HRPO assigned #	Target required for clinical significance	Local IRB submission status	Submitted/ approved by Advarra sIRB	Submitted/ approved by DoD HRPO	# of subjects screened/original planned target	# of patients enrolled/original planned target
Spectrum Health System	Not assigned yet	16	Approved	Submitted 10/5/21	Not available yet		
St. Mary's Medical Center	Not assigned yet	16	Approved	Submitted 8/17/21	Not available yet		
Rhode Island Hospital, Brown University	Not assigned yet	16	Approved	Submitted	Not available yet		
University of Colorado Department of Orthopaedics	Not assigned yet	16	Approved	Submitted 9/13/21	Not available yet		
Texas Tech University Health Sciences Center	Not assigned yet	16	Approved	Submitted 10/5/21	Not available yet		
Wake Forest University Baptist Medical Center	Not assigned yet	16	Approved	Submitted 10/5/21	Not available yet		
Inova Fairfax Hospital	Not assigned yet	16	Approved	Pending	Not available yet		
University of Oklahoma	Not assigned yet	16	Approved	Pending	Not available yet		
Jamaica Hospital Medical Center	Not assigned yet	16	Approved	Pending	Not available yet		
Grant Medical Center	Not assigned yet	16	Submitted	Not available yet	Not available yet		
Boston Medical Center	Not assigned yet	16	Submitted	Not available yet	Not available yet		
Virginia Commonwealth University	Not assigned yet	16	Submitted	Not available yet	Not available yet		
Vanderbilt University Medical Center	Not assigned yet	16	Submitted	Not available yet	Not available yet		
Walter Reed National Military Medical Center	Not assigned yet	16	Submitted	Not available yet	Not available yet		
University of Maryland, Shock Trauma Center	Not assigned yet	16	Submitted	Not available yet	Not available yet		
Sanford Health	Not assigned yet	16	Submitted	Not available yet	Not available yet		
MH Mission Health Hospital	Not assigned yet	16	Pending	Not available yet	Not available yet		

Site name	HRPO assigned #	Target required for clinical significance	Local IRB submission status	Submitted/ approved by Advarra sIRB	Submitted/ approved by DoD HRPO	# of subjects screened/original planned target	# of patients enrolled/original planned target
Emory University School of Medicine	Not assigned yet	16	Pending	Not available yet	Not available yet		
Eskenazi Health	Not assigned yet	16	Pending	Not available yet	Not available yet		
Louisiana State University	Not assigned yet	16	Pending	Not available yet	Not available yet		
Yale New Haven Hospital	Not assigned yet	16	Pending	Not available yet	Not available yet		
University of Texas Southwestern Medical Center	Not assigned yet	16	Pending	Not available yet	Not available yet		
University of Michigan	Not assigned yet	16	Pending	Not available yet	Not available yet		
Stanford University Medical Center	Not assigned yet	16	Pending	Not available yet	Not available yet		
Temple University Hospital	Not assigned yet	16	Pending	Not available yet	Not available yet		
University of California, LA	Not assigned yet	16	Pending	Not available yet	Not available yet		
University of Virginia Medical Center	Not assigned yet	16	Pending	Not available yet	Not available yet		
University of Alabama at Birmingham	Not assigned yet	16	Pending	Not available yet	Not available yet		
UC Irvine	Not assigned yet	16	Pending	Not available yet	Not available yet		
Harvard Orthopaedic Trauma Service	Not assigned yet	16	Pending	Not available yet	Not available yet		
University of Southern California	Not assigned yet	16	Pending	Not available yet	Not available yet		
University Hospitals Cleveland	Not assigned yet	16	Pending	Not available yet	Not available yet		
University of Pennsylvania	Not assigned yet	16	Pending	Not available yet	Not available yet		
Loyola Medical Center	Not assigned yet	16	Pending	Not available yet	Not available yet		