AWARD NUMBER: W81XWH-22-1-0937

TITLE: Intramedullary Calcium Sulfate Antibiotic Depot for Prevention of Open Fracture-Related Infection: A Randomized Clinical Trial

PRINCIPAL INVESTIGATOR: Jessica C Rivera, MD, PhD

CONTRACTING ORGANIZATION: LSU Health Sciences Center, New Orleans, LA

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PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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4. TITLE AND SUBTITLE

Intramedullary Calcium Sulfate Antibiotic Depot for Prevention of Open Fracture-Related Infection: A Randomized Clinical Trial

5a. CONTRACT NUMBER
W81XWH-22-1-0937

5b. GRANT NUMBER
OR210105

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Jessica C Rivera, MD

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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

LSU Health Sciences Center – New Orleans
433 Bolivar Street
New Orleans, LA 70112-7021

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
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10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The successful treatment of bone infection is improved by both local and systemically administered antibiotics. One method for local application of antibiotic to bone is via the simple use of clinically available calcium sulfate (CS) bone void fillers mixed with antibiotic and instilled into the medullary canal. This randomized clinical trial will enroll 494 patients at partnering level 1 trauma centers who have sustained a Type II or III open tibia fractures and who will be definitively treated with intramedullary nail (IMN) for fracture fixation. The patients will be randomized to either prophylactic intramedullary calcium sulfate antibiotic depot prior to IMN placement (CS) or to standard of care IMN (SN) without intramedullary antibiotics.

15. SUBJECT TERMS
Musculoskeletal System; Injury; Infectious Diseases & Agents

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRDC
Unclassified	Unclassified	Unclassified	Unclassified	21	**19b. TELEPHONE NUMBER** *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

The successful treatment of bone infection is improved by both local and systemically administered antibiotics. One method for local application of antibiotic to bone is via the simple use of clinically available calcium sulfate (CS) bone void fillers mixed with antibiotic and instilled into the medullary canal. This randomized clinical trial will enroll 494 patients at partnering level 1 trauma centers who have sustained a Type II or III open tibia fractures and who will be definitively treated with intramedullary nail (IMN) for fracture fixation. The patients will be randomized to either prophylactic intramedullary calcium sulfate antibiotic depot prior to IMN placement (CS) or to standard of care IMN (SN) without intramedullary antibiotics.

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

Musculoskeletal System; Injury; Infectious Diseases & Agents

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.

Major Task 1: Study Initiation—initially scheduled over 9 months on SOW for all sites. IND is approved and the single site IRB has approved the protocol.

Major Task 2: Enroll and Follow Patients in Clinical Trial—includes 1 year follow up for 494 subjects. Enrollment has not yet begun. We anticipate this will be possible in the first quarter of FY 24 at LSUHSC and Atrium and the additional sites to onboard in the new calendar year.

Major Task 3: Data Analysis—this task has not yet begun

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.

Accomplishments to date have included regulatory requirements. Prior to IRB submission, an IND had to be approved. This took several months including three rounds of responses leading up the IND approval 165174. In the meantime, the protocol was finalized, DSMB appointed, and RedCap data pilot entry developed. Following IND approval, the protocol was submitted to the single site IRB at Wake Forest Health Sciences and received approval on 22 SEP 23.

Activities not accomplished during this time includes the initial site HRPO approvals and enrollment initiation. With the above lengthy initial requirements met, we are poised to start catching up to get prime and sub site approvals and site initiations soon followed by subsequent site initiations. HRPO submission for LSUHSC and Atrium Health sites have been submitted.

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.

Now that we have an approved IND and the single site IRB approvals, we need to get enrollment started. This will be initiated at the prime (LSUHSC) and sub (Atrium) sites first. These two sites have submitted for HRPO approval. During this time, site initiation paperwork will be dispersed to the planned additional study sites to begin on boarding.

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:*

No changes in approach were required.

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.

There was a delay on the prime side contributing to the initial regulatory documents as the LSUHSC was not allowing any pre-IRB approval monies to be spent or hiring actions to be allowed. This limited the PI considerably; however, the Atrium team was very supportive and continued to work with the PI to get the IND approval accomplished. A new local policy was created to secure pre-IRB fund movement which allowed the PI to hire a research coordinator who has been instrumental in completing the IRB reliance submission and compiling the local HRPO documents. At this time, there are no additional problems to report.

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.

Because of the above, spending for the first year has been less than anticipated. This is not because the work has not been ongoing but due to limitations within the Sponsored Projects office at LSUHSC. A new policy was created to secure and track pre-IRB funds which allowed the PI to hire a research coordinator in the last quarter of FY23 and initiate subaward to Atrium.

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".

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: Dr. Jessica C Rivera, MD, PhD
Project Role: PI
Researcher Identifier (e.g. ORCID ID): 0000-0002-0967-2968
Nearest person month worked: 0.2 (calendar)
Contribution to Project: Dr. Rivera worked with Atrium Health on the responses to the FDA review of the IND submission. The protocol was finalized, submitted, and approved by the Wake Forest IRB and LSUHSC Reliance agreement signed.

Name: Carolyn Bridgman
Project Role: Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2.0 (calendar)
Contribution to Project: Once Carolyn onboarded, she assisted Dr. Rivera in the local trial preparation and HRPO documents.

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:
<u>Organization Name:</u>
<u>Location of Organization: (if foreign location list country)</u>
<u>Partner's contribution to the project</u> (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.*

Organization Name: Atrium Health Musculoskeletal Research Institute
Location of Organization: (if foreign location list country) Charlotte, NC
Partner's contribution to the project (identify one or more): The Atrium team is our main collaborator for the trial, serving as the trial coordinating center. The local PI, Dr. Rachel Seymour, has directed her team to include Dr. Megan Wally and CRC Christine Churchill through assisting Dr. Rivera with the FDN IND submissions and submitted the finalized protocol the the Wake Forest IRB. Subaward paperwork is in the works per the original statement of work for the Atrium team.

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.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.

Appendix document 1: FDA approval of IND
Appendix document 2: Wake Forest IRB approval of protocol
Appendix document 3: PHS Inclusion Enrollment Report

IND 165174

REMOVE FULL CLINICAL HOLD

Jessica C. Rivera, MD, PhD
Clinical Associate Professor
Department of Orthopaedic Surgery
Louisiana State University Health Sciences Center
433 Bolivar Street
Room 524 CSRB
New Orleans, LA 70112

Dear Dr. Rivera:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 1g of Vancomycin Powder, 1.2g of Tobramycin Powder, and Calcium Sulfate for prevention of open fracture related infection.

We also refer to your amendments dated May 18, 2023, June 12, 2023, and June 15, 2023, which provide a complete response to our May 2, 2023, letter which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submissions and have concluded that the clinical trial may be initiated.

If you have any questions, please contact Jennifer Grant, MSHS, Regulatory Project Manager, at jennifer.grant@fda.hhs.gov or (301) 796-0480.

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER W KIM
06/16/2023 09:58:28 AM

WAKE FOREST
UNIVERSITY
HEALTH SCIENCES

Office of Research
INSTITUTIONAL REVIEW BOARD.

MEMORANDUM

To: Rachel Seymour
Atrium/Carolinas Healthcare System

From: Thomas Pranikoff, Chair, WFUHS IRB Board 3
Institutional Review Board

Date: 9/22/2023

Subject: Human Protocol: IRB00092183
Intramedullary Calcium Sulfate Antibiotic Depot for Prevention of Open Fracture Related Infection: A Randomized Clinical Trial

Study Documents:
Protocol Version: CaS04 Protocol_V1_Clean.docx; Informed Consent Version: CaS04_Consent_v1_Clean.docx; Investigator's Brochure: 060180s047lbl_vanco.pdf, 062366s033lbl_gentamin.pdf; Advertisements: IND 165174_Remove Full Clinical Hold (COR-INDHOLD-05).pdf; Advertisements: 060180s047lbl_vanco.pdf, 065013s007lbl_Tobra.pdf; Other Documents: IPAQ.pdf, PROMIS-29 Profile v2.0.pdf, Veterans RAND 12 (VR-12).pdf

The Institutional Review Board (IRB) has approved the above-named protocol and study documents, after review at a convened meeting on 9/6/2023. A submission requesting renewal together with a summary progress report must be submitted to the Board at least one month prior to 9/5/2024.

This submission has met the requirements of the 2019 Common Rule.

This approval includes a limited waiver of HIPAA authorization to identify potential subjects for recruitment into this research study, as allowed under 45 CFR 164.512. This temporary waiver provides access to protected health information (PHI) to confirm eligibility and facilitate initial contact, after which consent and HIPAA autorization will be sought. Access and use is limited to the minimum amount of PHI necessary to review eligibility criteria and to contact potential subjects.

Federal regulations and Board policy require that you promptly report to the Board for review/approval:

- Proposed changes in the research activity (e.g., protocol amendments; consent form revision; advertisements). Changes may not be initiated without IRB review and approval, unless necessary to eliminate an immediate hazard to subjects.

- Serious adverse events and unanticipated problems involving risks must be reported to the Board, institutional officials, FDA, sponsor and other regulatory agencies as required by the protocol, local policy and state or federal regulation.

Please provide a final report to the Board when the project is completed and Board approval can be terminated.

The Wake Forest School of Medicine IRB is duly constituted, has written procedures for initial and continuing review of clinical trials; prepares written minutes of convened meetings, and retains records pertaining to the review and approval process; all in compliance with requirements of FDA regulations 21 CFR Parts 50 and 56, HHS regulations 45 CFR 46, and International Conference on Harmonisation (ICH) E6, Good Clinical Practice (GCP), as applicable. WFSM IRB is registered with OHRP/FDA; our IRB registration numbers are IRB00000212, IRB00002432, IRB00002433, IRB00002434, IRB00008492, IRB00008493, IRB00008494, and IRB00008495.

WFSM IRB has been continually fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) since 2011.

Medical Center Boulevard, Winston-Salem, NC 27157-1023 (336) 716-4542 / fax (336) 716-4480

OMB Number: 0925-0770
Expiration Date: 09/30/2024

PHS Inclusion Enrollment Report

1. * Inclusion Enrollment Report Title

Intramedullary Calcium Sulfate Antibiotic Depot for Prevention of Open Fracture-Related Infection: A Randomized Clinical Trial

2. * Using an Existing Dataset or Resource ☒ Yes ☐ No

3. * Enrollment Location Type ☒ Domestic ☐ Foreign

4. Enrollment Country(ies)

USA: UNITED STATES

5. Enrollment Location(s)

LSUHSC, Atrium Health

6. Comments

Planned enrollment informed by prior clinical trial enrollment at Carolinas Medicine Center (Atrium Health)

Planned

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	3	0	0	4
Asian	3	4	0	0	7
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	54	123	3	10	190
White	84	196	2	5	287
More than One Race	1	5	0	0	6
Total	143	331	5	15	494

Cumulative (Actual)

Racial Categories	Ethnic Categories									
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			Total
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0