Award Number: W81XWH-15-2-0088

TITLE: Pathomechanics of Post-Traumatic OA Development in the Military Following Articular Fracture

PRINCIPAL INVESTIGATOR: Dr. Jessica C. Rivera

CONTRACTING ORGANIZATION: The Geneva Foundation
Tacoma, WA 98402

REPORT DATE: October 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick,
Maryland 21702-5012

DISTRIBUTION STATEMENT:

Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
OCT 2017	Annual	30 Sep 2016 - 29 Sep 2017

4. TITLE AND SUBTITLE
Pathomechanics of Post-Traumatic OA Development in the Military Following Articular Fracture

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-15-2-0088

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Dr. Jessica Rivera

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Geneva Foundation
917 Pacific Ave., Ste. 600
Tacoma, WA 98402

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Ft Detrick, MD 21702-5012

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 objective of the proposed research is to develop new models for predicting the risk of post-traumatic osteoarthritis (PTOA) following intra-articular fracture (IAF). Aim 1, pursued this year, involved evaluating pre- and post-treatment CT data from patients with combat-related IAFs to measure fracture severity and post-reduction contact stress exposure. This study is being conducted in collaboration with the University of Iowa (PI: Donald Anderson, PhD) who is conducting these calculations on patients identified at the U.S. Army Institute of Surgical Research. IRB and HRPO approval has been obtained at both sites. Ongoing screening of potential subjects identified through the Department of Defense Trauma Registry has resulted in 64 fractures transferred and studied by the U of Iowa.

Our partners at the U of Iowa continue to work on related efforts in civilian trauma patients to refine the measuring techniques. The military subjects pose some unique challenges in terms of injury severity but we remain confident that our collaborator's skill in imaging analysis will remain successful as we study our military patients.

15. SUBJECT TERMS: Post-osteoarthritis, CT-based analysis, intra-articular fractures

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
			Unclassified	8	USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified			

Table of Contents

Page

Introduction:

The objective of this research is to develop new models for predicting the risk of post- traumatic osteoarthritis (PTOA) following intra-articular fracture (IAF). Our collaborators at the University of Iowa previously developed capabilities to predict PTOA risk from acute fracture severity (measured from pre-op CT) and chronic elevated contact stress (post-op CT) associated with IAFs, but more patient data are needed to make the risk models clinically useful. Prospective studies of PTOA development following IAFs face many challenges. Severe IAFs are not frequently seen in civilian practice, making it difficult to accrue sufficient numbers for clinical study. An added challenge is that in order to determine if a patient develops PTOA, they may need to be followed for years into the future, threatening subject retention. One of the attractive features of the CT-based measures of mechanical factors pioneered by the Initiating PI (Anderson) is that retrospective studies can include patients who were injured years in the past. Recent military conflicts, which unfortunately produced a substantial number of severe fractures, including IAFs, provide a unique opportunity to overcome these challenges and to honor the military personnel who sustained combat-related IAFs. Given their prevalence and severity, and the degree to which these injuries impact long- term function of injured service members, better methods to predict PTOA risk would benefit our current generation of new veterans, as well as future service members at risk for IAF.

Keywords:

Post-traumatic osteoarthritis, CT analysis, intra-articular fractures

Accomplishments:

What were the major goals of the project?

The Statement of Work includes 6 major tasks over 3 Specific Aims:

Specific Aim 1: Evaluate pre- and post-treatment CT data from patients with combat-related IAFs to measure fracture severity and post-reduction contact stress exposure	
Major Task 1: Regulatory Approval	Months
Subtask 1.1: Obtain local IRB	1-3
Subtask 1.2: Obtain HRPO approval	4-6
Milestone #1: Regulatory approval received	5-6
Major Task 2: Adapt CT Analysis Methods	Months
Subtask 2.1: Obtain representative CT studies	3
Subtask 2.2: Trial analysis methods with CT studies	1-3
Subtask 2.3: Modify analysis methods as needed	3-9
Milestone #2: Co-author manuscript on methods to analyze combat-related IAFs	9-12
Major Task 3: Subject Identification	Months
Subtask 3.1: Obtain potential subject list with demographic and injury data from DoDTR	7
Subtask 3.2: Screen available CT scans for requisite images for inclusion	8-12
Milestone #3: Subject list finalized	12
Major Task 4: CT Calculations	Months
Subtask 4.1: De-identified CDs compiled and express mailed from Site 2 to Site 1	9-13
Subtask 4.2: CT calculations for injury severity and post-reduction contact stresses	10-18
Milestone #4: Co-author manuscript on fracture severity and post-reduction contact stress measures in patients with combat-related IAFs	18-24

Specific Aim 2: Measure the occurrence of PTOA up to ten years following fracture reduction surgery	
Major Task 5: PTOA radiographic frequency	Months
Subtask 5.1: Identify radiographs for KL grading; multiple investigators do KL grading	9-14
Milestone #5: Co-author paper detailing PTOA incidence and grading for patients with combat-related IAFs	16-20

Specific Aim 3: Quantify the extent to which fracture severity and post-reduction contact stress predict PTOA	
Major Task 6: PTOA symptoms and quality of life	Months
Subtask 6.1: Identify subjects' contact information through DoD and/or VA sources	12-16
Subtask 6.2: Conduct prospective contacting of subjects for outcomes questionnaires	12-28
Milestone #6: Co-author manuscript detailing symptoms and treatment timelines for patients with combat-related IAFs	25-32
Subtask 6.3: Correlate CT-based analysis results with KL grade/PTOA status, questionnaire outcomes, and various radiographic results	28-32
Milestone #7: Co-author manuscript detailing relationships between CT-based results and PTOA outcomes – PTOA risk model	32-36

What was accomplished under these goals?
Major Task 1 is completed (USAISR Protocol Number H-15-022, HRPO Log Number A-18857, IRB Protocol Number M-10466) as of October 2015.

Major Task 2 is underway. Our collaborators at the University of Iowa continue to refine the CT analysis methodology and have successfully disseminated their results in this work on civilian trauma subjects via two accepted manuscripts and one submitted abstract. This work will support the methods paper for the unique challenges posed by the CT analysis of military subjects.

Major Task 3 is underway. After receipt of the potential subject list by way of Department of Defense Trauma Registry (DoDTR) request, we immediately began screening subjects for inclusion and exclusion criteria. A total of 57 subjectswith 64 fractures have been identified for inclusion and are considered "enrolled." Additional subjects continue to be screened.

Major Task 4 is underway. CDs containing CT imaging from enrolled subjects are being sent to U of Iowa once they are checked and confirmed to be de-identified. As the CT cases are received there, Dr. Anderson's lab is performing calculations of injury severity and post reduction contact stress.

Major Task 5 is underway at our local site. As subjects are screened in, we are abstracting the DoD electronic medical record to examine the care received for the injured joint for as long as the subjects are seen within the DoD health care system.

Major Task 6 initial steps are currently being planned.

What opportunities for training and professional development has the project provided?
Nothing to report.

How were the results disseminated to communities of interest?
The results of the first 15 subjects analyzed was presented at the Limb Lengthening and Reconstruction Society annual meeting (July 2017, Park City, UT) and the Military Health System Research Symposium (August 2017, Orlando, FL).

What do you plan to do during the next reporting period to accomplish the goals?
We will continue screening subjects and including those who meet study criteria. This will result in additional subjects' CT images being transferred to Dr. Anderson's lab for analysis. We will also continue data abstraction for Major Task 5 in the DoD electronic medical record.

Impact

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report; however, the end result of this project will contribute to discipline of PTOA prediction based on CT metrics.

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.

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
Nothing to report.

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
Not applicable.

Products:

Publications, conference papers, and presentations
Podium presentation: Limb Lengthening and Reconstruction Society annual meeting (July 2017, Park City, UT)
Podium presentation: Military Health System Research Symposium (August 2017, Orlando, FL)

Website(s) or other Internet site(s)
Nothing to report.

Technologies or techniques
Nothing to report from this site directly from these data. The CR analysis techniques previously described by Dr. Anderson will face specific required modifications as they are applied to military subjects due to the severity of the injury and multiple fractures typical of combat injuries.

Inventions, patent applications, and/or licenses
Nothing to report.

Other Products
Nothing to report.

Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Jessica Rivera
Project Role:	PI
Nearest person month worked:	0.60

Contribution to Project:	MAJ Rivera serves as the site study PI on this research project for the study's partnering PI option. She will provide the necessary programmatic leadership, administrative oversight and support for all aspects of the proposed work to be conducted at ISR/SAMMC site, ensuring that personnel and departmental resources are properly aligned to achieve the goals of this study. She meets with the study personnel and communicates with the partnering site on a regular basis to review planning and execution of the proposed project. Finally MAJ Rivera will be responsible for the preparation of technical reports, manuscripts, and other dissemination materials generated by this study.
Name:	Allyson Corona
Project Role:	Research Coordinator
Nearest person month worked:	6
Contribution to Project:	Ms. Corona is responsible for the day-to-day operations of the study. She will be responsible for assisting compilation of radiographic images and chart abstraction. She will also assist with the preparation of all study related correspondence and technical reports, maintain research files and data, procure study supplies and coordinate all procurement requests through The Geneva Foundation, and ensure budgetary adherence.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report.

What other organizations were involved as partners?
Nothing to report.

Special Reporting Requirements

COLLABORATIVE AWARDS: The Collaborating PI at U of Iowa (Dr. Donald Anderson) is submitting a separate progress report for that site.

Appendices

Quad chart, updated 20OCT2016

Pathomechanics of Post-Traumatic OA Development in the Military Following Articular Fracture

W81XWH-15-2-0088

PI: Jessica Rivera, M.D. **Task Area: ETRM** **Award Amount:** $240K

Study/Product Aim(s)

- Aim 1. Determine the proportion and timing of PTOA radiographic development in lower extremity IAFs following combat injury
- Aim 2. Evaluate pre- and post-treatment plain radiography and computed tomography (CT) data from IAF fracture patients to measure fracture severity and post-reduction contact stress.
- Aim 3. Measure the occurrence of PTOA up to ten years following fracture reduction surgery, and quantify the extent to which fracture severity and post-reduction contact stress predict PTOA.

Approach

Subjects identified by the DoDTR with lower extremity intra-articular fracture will be abstracted for the outcomes of PTOA development clinically and radiographically. Pre fixation and post fixation CT images will be shared with U of Iowa for fracture energy and contact stress calculations. These calculations will be tested for association with PTOA outcome.

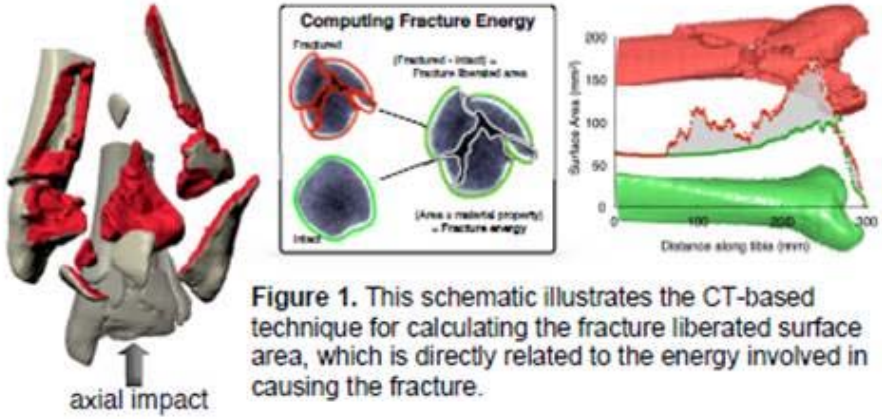

Figure 1. This schematic illustrates the CT-based technique for calculating the fracture liberated surface area, which is directly related to the energy involved in causing the fracture.

Timeline and Cost

Activities	FY15	FY16	FY17	FY18
IRB approval				
Data Collection (local)				
Data Compilation (collaborator)				
Analysis and Dissemination				
Proposed Budget/Year	$50	$64	$64	$63
Expended Budget/Year	$7	$20.6	$106	$106

Completed In Progress Pending

Goals/Milestones

CY16 Goal – Regulatory and Start up

- ■ IRB and HRPO approval
- ■ Hiring actions and CRADA with U of Iowa
- ■ Begin protocol

CY17 Goals – Data Collection/Sharing

- ▨ Continue local data collection
- ▨ Compile CT metrics data from collaborative site (U of Iowa)

CY18 Goal –

- ☐ Complete local data collection
- ☐ Continue analyses to ascertain statistical power and to identify salient pathological outcomes

Comments/Challenges/Issues/Concerns

None

Budget Expenditure to Date

Total Proposed Expenditure: $240K

Total Actual Expenditure: $93.8K

Updated: (October 20, 2017)