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TITLE: Evaluation of the Diagnostic and Therapeutic Value of Tissue Ultrafiltration in Patients at Risk of Acute Compartment Syndrome (ACS)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Objective: This application proposes a randomized clinical trial (RCT) to validate tissue ultrafiltration (TUF) as means of diagnosing and preventing acute compartment syndrome (ACS) in a manner that can be used in austere environments and in prolonged field care (PFC) situations. The efficacy of TUF will be evaluated in 4 different ways with one primary hypothesis and three secondary hypotheses. TUF is hypothesized to reduce the likelihood of ACS, fasciotomy incidence, intramuscular pressure (IMP), and functional outcomes at 6 months. In addition, exploratory goals are to test the impact of TUF on improving muscle strength and to evaluate the diagnostic performance of serial measurement of biomarkers related to muscle metabolism in the interstitial fluid. **Study Design**: RCT of 200 patients treated at one of 4 sites comparing standard of care therapy plus TUF to standard of care therapy alone in a cohort of patients at risk for acute compartment syndrome after leg injury. **Military Benefit/ Clinical Impact**: This proposal's goal is to validate a method to diagnose and manage ACS that is ideally suited to PFC. The insertion of TUF catheters that connect to a simple closed suction source could be easily accomplished by a combat medic, allowing for immediate prophylactic therapy. Further, IMP measurements can be obtained, and metabolic monitoring of the limb can be performed. A more precise and confident diagnosis of impending ACS would allow accurate triage of these patients who need urgent surgery, versus continued field care in patients that are stable.

15. SUBJECT TERMS
USAMRAA Terms and Conditions

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Introduction

Acute compartment syndrome (ACS) is a well-known complication of extremity injury that occurs in both civilians and among military combat casualties. The pathophysiology is understood to be related to a progressive and sustained increase in intracompartment pressure in the injured extremity, with resultant impairment of myoneural perfusion. If the process is not diagnosed and treated with immediate fasciotomy, permanent myoneural damage will occur. Unfortunately, no definitive diagnostic standard exists. The diagnosis is typically made by noting that the affected patient is experiencing ischemic pain in the involved muscles, which may be very difficult to differentiate from pain caused by the underlying injury. Since early fasciotomy is currently the only effective treatment, precise diagnosis is necessary to avoid both the sequelae of missed compartment syndrome as well as unnecessary fasciotomy. These clinical issues are even more profound for our military health system, which must manage combat casualties in austere environments, possibly without immediate access to surgical care. Methods that improve the diagnosis of ACS and which may provide prophylactic or even therapeutic treatment in the early stages of ACS would be a major advance in the care of all trauma patients. For the military, an approach that would be available in a prolonged field care situation that would allow immediate and precise identification of ACS would facilitate optimized allocation of resources so that evacuation for emergency surgical care is done only when needed. This application proposes a randomized clinical trial (RCT) to validate tissue ultrafiltration (TUF) as means of diagnosing and preventing acute compartment syndrome (ACS) in a manner that can be used in austere environments and in prolonged field care (PFC) situations. The efficacy of TUF will be evaluated by assessing the likelihood of ACS as determined by an independent expert panel, fasciotomy incidence, the level of intramuscular pressure (IMP), and functional outcomes at 6 months.

Keywords: extremity trauma, acute compartment syndrome, fasciotomy, intracompartment pressure, tissue ultrafiltration.

Accomplishments:

- **What were the major goals of the project?**

Major Task 1: Study Initiation. This task includes 11 subtasks as listed below, with their milestones and status regarding completion.

Subtask 1: Occam completes safety testing and lists themselves as manufacturer of the catheter, which is a class I device, months 1-11. Status: Completed.

Subtask 2: Program and pilot test REDCap, the web-based system used for electronic data capture in all METRC studies, Months 7-10. Status: Completed.

Subtask 3: Develop SOPs for fluid removal and monitoring protocol. Months 7-10. Status: Completed.

Subtask 4: Finalize protocol, data collection protocols, Months 9-10. Status: Completed

Subtask 5: Obtain initial sIRB approval at JH, months 11-12. Status: In progress, 25% complete. The IRB application was submitted to the Johns Hopkins University (JHU) sIRB in Quarter 5 and remains under review. During Q6, the legal compliance officers for the JHU sIRB asked about the combined use of our tissue ultrafiltration catheter (which at that time was not registered with the FDA) and the Hemovac drain (a 510(K)-exempt device) and requested that we obtain non-significant risk (NSR) determination or an investigational device exemption (IDE) from the FDA. Our research team contacted the FDA ombudsman, and we were provided an FDA guidance document indication that the combined use of two separate FDA cleared devices was acceptable, if

the devices were used in accordance with their Instructions for Use, which is the case in our study. This information was provided to the JHU sIRB compliance officers, but they still asked for formal FDA determination of NSR status or an approved IDE before they would review our IRB application. In March 2022, we consulted with the regulatory officer and the program officer at HRPO and determined that a request for NSR determination from the FDA was the most appropriate approach. Now that the TUF catheters are registered with the FDA, our research team is preparing a Q-submission to the FDA, which will be submitted in October 2022 (the beginning of Q9). The NSR determination should be completed by the end of Q9, and depending on the timing of that, we now anticipate sIRB approval at the end of Q9 or in Q10.

Subtask 6: Submit approved protocol to USAMRMC HRPO for review, months 12-13. Status: Not done, waiting for JHU sIRB approval and will be initiated as soon as that occurs, most likely in Q10.

Subtask 7: Establish and execute reliance agreements with all participating centers. Status: Completed.

Subtask 8: USAMRMC Human Research Protections Office review and approval of site-specific IRB-approved human use documents, months 13-15. Status: Not yet started. Study documents are currently under review by the Johns Hopkins sIRB and will be submitted to USAMRMC HRPO when the local review is completed, which will be at the end of Q9 or Q10. We therefore anticipate USAMRMA CRPO approval to follow in late Q10 or early in Q11.

Subtask 9: Develop training materials for Research Coordinators on study procedures and data collection. Training materials will include webinar-based training sessions, written guidance documents posted to the METRC website and standard operating procedure templates, months 12-13. Status: Started, 75% complete.

Subtask 10: Train Research Coordinators on study procedures and data collection (in-person meeting). Status: Not yet started; now anticipated to be done in Q10, coincident with final IRB approval.

Subtask 11: Certify sites to begin screening and enrolling patients. Status: Not yet started; now anticipated to be done in Q10, coincident with final IRB approval.

Subtask 12: Conduct study initiation calls to review study procedures prior to initiation of screening and enrollment activities. Status: Not yet started; now anticipated to be done in Q10, coincident with final IRB approval.

Major Task 2: Enroll and Follow Patients, months 18-33. Status: Patient enrollment was to begin in Q7, but is behind schedule due the delays in TUF manufacturing and Human Subjects Research Approval. We now anticipate beginning to enroll patients in Q10 or early Q11.

Major Task 3: Data Analysis, months 34-36. No planned work in Y1.

- **What was accomplished under these goals?**

All study activities performed during Year 2 were primarily related to working with our device manufacturer (Occam Design) to complete device safety studies and then register the TUF catheter with the FDA, which was completed during Q8. As this work neared completed, the research team prepared a Q-Submission to the FDA during Q8. Refinement of the study protocol and the REDCap data collection system was completed.

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 primary goal during the next reporting (Year 3) is to initiate the clinical study. This will require obtaining initial protocol review and approval from the Johns Hopkins sIRB, followed by submission to USAMRMC HRPO for review and approval. Finally, site specific IRB approvals will need to be obtained. Coincident with this work, all necessary case report forms and our web-based data repository (REDCap) will be finalized once we determine whether we need to incorporate any feedback from the IRB or HRPO. The goal is to complete this activity in Q10, which represents a one-year delay from our SOW. During Q10, we plan to complete site personnel education and training, with the goal of initiating patient recruitment and enrollment at four clinical sites in Q11. Finally, as patient enrollment commences, clinical site monitoring will also be initiated to ensure compliance with all protocols and data integrity.

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.

CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

  Our original statement of work included several regulatory tasks, namely submitting a request to the FDA for NSR determination for the combined use of the TUF catheter and closed suction device according to their proposed use in our clinical trial; for design validation testing to support a 510(k) transfer for the TUF catheter to Occam Design, and finally to apply for the 510(k) transfer for TUF catheter to Occam Design. As reported in our Year 1 Annual report, it was determined during Y1 that a different regulatory approach was appropriate, namely registration of the TUF device with the FDA as a class one device manufactured by Occam Design. A revised statement of work approved during Y1. In Year 2, work proceeded according to our revised SOW.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  During Y1 and Y2, the manufacturer of the TUF catheters needed for this study, Occam Design, encountered several supply chain and manufacturing issues that delayed their progress in completing the necessary design validation testing. This work is now completed. The next step is obtaining the necessary human subjects research approvals, which will require working with multiple entities including gaining the NSR determination from the FDA, and approvals from the JHU sIRB, the USAMRMC Human Research Protections Office, and the IRBs at the local sites. We do not know how long this will take, but with the device registration completed and once the NSR determination from FDA is received, we hope this work can all be completed, and patient enrollment begun in Q10. This is delayed a year form our initial plan. We hope to complete all patient enrollment in Q11 and 12, and the analysis work in an extension period (Y4).

- **Changes that had a significant impact on expenditures**

  Based on the delays described above, study activities and site payments that were expected to be paid for work done in Y1 and Y2 will instead be realized in year 3 of the project, when the work is done. Our expenditures during the first two years of performance are therefore lower than originally anticipated, and we have adjusted effort and other expenses to reflect the updated timeline and implementation of study activities. This slower period of expenditure does not impact the total anticipated expenses for the study, only the timing of spending.

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

  Nothing to report.

- **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.

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.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	*Andrew Schmidt*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-9740-4049*
Nearest person month worked:	*1.10*
Contribution to Project:	*Dr. Schmidt, as study PI, participated in weekly meetings and contributed to developing the study protocol.*
Funding Support:	*N/A*

Name:	*Renan Castillo*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-9889-4046*
Nearest person month worked:	*0.36*
Contribution to Project:	*Dr. Castillo, as PI at the METRC Coordinating Center, participated in weekly meetings as needed and contributed to developing the study protocol, as well as supervising grant related work at the MCC.*
Funding Support:	*N/A*

Name:	*Katherine Frey*
Project Role:	*Clinical Research Manager*
Researcher Identifier (e.g. ORCID ID):	*0000-0001-5305-1774*
Nearest person month worked:	*0.42*
Contribution to Project:	*Dr. Frey, as Program Director, participated in weekly meetings and contributed to developing the study protocol, worked on the JH sIRB submission, and performed work related to coordinating study onboarding at the 4 clinical study sites.*
Funding Support:	*N/A*

Name:	*Dana Alkhoury*
Project Role:	*Project Director*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*1.44*
Contribution to Project:	*Managed protocol development; developed RedCAP CRFs and SOPs for clinical sites; contributed to JH sIRB submission.*
Funding Support:	*N/A*

- **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:**
- **QUAD CHARTS:**

APPENDICES: