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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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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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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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?**
    - *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. 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: Completed.

Subtask 6: Submit approved protocol to USAMRMC HRPO for review, months 12-13. Status: Completed

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: Completed.

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: Completed.

Subtask 10: Train Research Coordinators on study procedures and data collection (in-person meeting). Status: Completed.

Subtask 11: Certify sites to begin screening and enrolling patients. Status: In progress, 90% completed. Awaiting completion of RedCap for patient randomization and data submission.

Subtask 12: Conduct study initiation calls to review study procedures prior to initiation of screening and enrollment activities. Status: In progress, 90% completed. Awaiting completion of RedCap for patient randomization and data submission.

Major Task 2: Enroll and Follow Patients, months 18-33. Status: not started. Patient enrollment was to begin in Q7, but is behind schedule due the delays in TUF manufacturing and Human Subjects Research Approval. We have obtained a No-Cost Extension (NCE) and are expecting to begin enrollment in Q13.

Major Task 3: Data Analysis, months 34-36. Status, not started.

- **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.*

All study activities performed during Year 3 were related to obtaining the necessary regulatory and Human Subjects Research approvals for the study. At the end of Y2, the research team prepared a Q-Submission to the FDA during Q8. A non-significant risk determination was received from FDA on 2/15/23. Johns Hopkins sIRB approval was submitted and received on April 10, 2023. DOD HRPO approval was submitted during Q12 (approved 10/2/23). A 1-year NCE extension was requested and received on 9/4/23.

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."*

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."*

    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?**
    - *Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

    The primary goal during the next reporting (Year 4) is to initiate and complete the enrollment of the planned 200 patients. As patient enrollment commences, clinical site monitoring will also be initiated to ensure compliance with all protocols and data integrity.

IMPACT: *Describe 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.

CHANGES/PROBLEMS: *The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer 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:*

- **Changes in approach and reasons for change**
  - *Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.*

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 Years 2 and 3, work proceeded according to our revised SOW.

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.*

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. During Y3, the necessary human subjects research approvals were obtained, which included NSR determination from the FDA and human subject research approvals from the JHU sIRB, the USAMRMC Human Research Protections Office, and the IRBs at the local sites. A one-year NCE has been received, and the team will initiate patient enrollment with the goal to complete this in the extension period (Y4).

- **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.*

    Based on the delays described above, many study activities and site payments that were expected to be paid for work done in Y1 to Y3 will instead be realized in year 4 of the project, when the work is done. Our expenditures during the first three 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**

    - *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.*

    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: *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. In addition to a description of the technologies or techniques, describe how they will be 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. State whether an application is provisional or non-provisional and indicate the application number. 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;*
  - *biospecimen 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.

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."*

Name:	*Andrew Schmidt*
Project Role:	*Principal Investigator*
Researcher Identifier (e.g. ORCID ID):	*0000-0002-9740-4049*
Nearest person month worked:	0.63
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:	*0.60*
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:	*0.60*
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:	*1.20*
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: