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

PRINCIPAL INVESTIGATOR: Andrew H. Schmidt, M.D.

CONTRACTING ORGANIZATION: Hennepin Healthcare Research Institute  
Minneapolis, MN

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<b>14. ABSTRACT</b>  <b>Objective:</b> 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. <b>Study Design:</b> RCT of 200 patients treated at one of 5 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. <b>Military Benefit/ Clinical Impact:</b> 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.					
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## TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	6
5. Changes/Problems	6
6. Products	7
7. Participants & Other Collaborating Organizations	8
8. Special Reporting Requirements	9
9. Appendices	9

## 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, intra compartment 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: In progress, 50% complete. Based on most recent estimate from Occam, they expect to complete this in month 13-14 (Q5). This represents a 2-3 month delay that we will try to make up by performing tasks in parallel, so that patient enrollment can begin in months 17-18 as planned.

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

Status: Not yet started, now plan to be initiate and complete in Q5, just slightly behind schedule. This process is integrally connected to protocol development, SOP development, and the device instructions for use, and cannot be completed until these dependent activities are completed. However, the elements that will populate the data collection forms have been finalized and the delays in programming will not have impact on the overall progress of the study.

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: Delayed due to changes in the regulatory approach (Subtask 1). Now plan to obtain in Q5 once the TUF catheters are registered with the FDA. While we anticipate a 2 m review period with the Johns Hopkins sIRB, other projects recently submitted have taken up to 3 m for approval. Consequently, there is a possibility that this review process may take slightly more time than anticipated, which will impact other tasks that depend on completion of this subtask. We will continue to keep the study science officer and project officer apprised of any delays on this front. We have met with sIRB staff to review our approach in an attempt to streamline our submission, and hope that these potential delays will not be realized.

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

Status: Not done, waiting for JH sIRB and will be initiated as soon as possible, ideally Q5 to Q6.

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

Status: Completed.

Subtasks 8-12: Status: no planned work in Y1.

Major Task 2: Enroll and Follow Patients, months 18-33. No planned work in Y1.

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

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

All planned study activities during year 1 were related to completing the clinical study protocol and working with our device manufacturer (Occam Design) so that the tissue ultrafiltration catheters necessary for the study would be available in time for intended patient enrollment to begin in month 18. During Q2, Occam Design determined that the regulatory pathway to allow the TUF catheters to be marketed and distributed was simpler than originally planned. Many of the subtasks included in our initial statement of work were no longer necessary. A revised statement of work was submitted April 30th, 2021 and approved by our study science officer and grant officer. The study protocol was finalized during Q4 and has been submitted to the Johns Hopkins single IRB. With respect to the second activity, Occam Design encountered several supply chain-related delays affecting their ability to manufacture and package the TUF catheters, but overcame those and is on track to complete device design validation testing and FDA product registration during Q5.

- **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 2) is to initiate the clinical study. This will require obtaining initial protocol review and approval from the Johns Hopkins sIRB and then submitting the approved protocol 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 created. The goal is to complete all of this during Q5 and Q6, consistent with our approved statement of work. During quarters seven and eight, we plan to complete site personnel education and training, and initiate patient recruitment and enrollment at four clinical

sites. One of our initially proposed sites, San Antonio Military Medical Center, recently let us know that they cannot participate in patient enrollment, but their site PI, Dr. Sarah Pierrie, will still participate in this study in an oversight manner, providing important military input. 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 initial 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. During Q2 of the study, it was determined that these steps were not necessary, and that simple registration of the device with the FDA as a class one device by Occam Design was all that was necessary. A proposed revision to our statement of work was submitted to our grant officer and our science officer and approved during Q3.

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

The manufacturer who will provide the ultrafiltration catheters for this study, Occam Design, encountered several supply chain issues affecting their ability to manufacture prototype devices, and then to package and ship the devices once ready package and ship the devices once ready. However, these issues have been resolved, but will contribute to a two to three months delay in having the devices ready for distribution. At the present time, it is not clear whether this will delay our patient enrollment that is slated to begin month 18.

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

Based on the delays described above, some study activities and site payments that were expected to be paid for work done in Y1 will instead be realized in year 2 of the project when the work is done. Our expenditures during the first year of performance are therefore lower than originally anticipated as 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.**

We recently wrote a paper explaining and validating our procedures for using expert panel review to identify cases of acute compartment syndrome (ACS), using the data from the original Predicating Acute Compartment Syndrome study. This paper will serve as a reference for this study when we describe our procedures for adjudicating cases of ACS in our study population. LeRoux et al. Defining Incidence of Acute Compartment Syndrome in the Research Setting: A Proposed Method From the PACS Study. J Ortho Trauma. In press.

- **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:	<i>Andrew Schmidt</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0002-9740-4049</i>
Nearest person month worked:	<i>0.36</i>
Contribution to Project:	<i>Dr. Schmidt, as study PI, participated in weekly meetings and contributed to developing the study protocol.</i>
Funding Support:	<i>N/A</i>

Name:	<i>Renan Castillo</i>
Project Role:	<i>Principal Investigator</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0001-9889-4046</i>
Nearest person month worked:	<i>1.20</i>
Contribution to Project:	<i>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.</i>
Funding Support:	<i>N/A</i>

Name:	<i>Katherine Frey</i>
Project Role:	<i>Project Director</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0001-5305-1774</i>
Nearest person month worked:	<i>0.84</i>
Contribution to Project:	<i>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.</i>
Funding Support:	<i>N/A</i>

Name:	<i>Dana Alkhoury</i>
Project Role:	<i>Study Manager</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>2.4</i>
Contribution to Project:	<i>Managed protocol development; developed RedCAP CRFs and SOPs for clinical sites; contributed to JH sIRB submission.</i>
Funding Support:	<i>N/A</i>

- **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:**