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TITLE: Pilot Study of Role of Continuous Tissue pH Measurement in the Diagnosis of Acute Compartment Syndrome

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<b>13. SUPPLEMENTARY NOTES</b>						
<b>14. ABSTRACT</b>  <b>Objective:</b> Demonstrate that continuous measurement of tissue pH (cIMpH) shows worsening values suggesting progressive acidosis in the injured limb, to correlate those data with the results of both detailed serial clinical assessments and continuous pressure monitoring data collected for the parent study, and to compare tissue pH in patients receiving TUF versus standard of care. <b>Study Design:</b> Observational study of 40 patients enrolled in a larger trial of patients with severe lower leg injuries at high-risk of ACS. Enrolled patients will receive cIMpH measurements in both legs, as well as the procedures mandated by the parent study (detailed serial clinical assessments, cIMP monitoring in the injured leg, and continuous TUF for patients randomized to the experimental arm of the parent study). <b>Military Benefit/Clinical Impact:</b> This proposal validates methods to diagnose and manage ACS that is ideally suited to care of the injured soldier in a prolonged field care scenario. The addition of cIMpH measurement in a subset of patients in the parent study will supply pilot data regarding efficacy of IMpH as a simple biomarker indicating whether tissue perfusion is adequate or becoming compromised, and that can be readily measured in austere environments and continued during medical evacuation and early patient resuscitation.						
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## Introduction

Acute compartment syndrome (ACS) is a well-known complication of extremity trauma, occurring when intramuscular pressure (IMP) becomes sufficiently elevated that capillary blood flow and tissue perfusion is reduced below a level necessary to sustain tissue viability. Once ACS develops and is diagnosed, the current standard of care is immediate fasciotomy, which reduces IMP, restores tissue perfusion, and prevents permanent muscle and nerve injury or amputation (when done early enough). If untreated, ACS results in irreversible myonecrosis, ischemic neuropathy, and occasionally rhabdomyolysis and renal failure. However, ACS is notoriously difficult to diagnose, and patients continue to undergo unnecessary fasciotomy while in other cases the diagnosis is missed. In both cases, the patient is subjected to the adverse sequelae of an unneeded fasciotomy or the myoneural damage that results from missed ACS. Improved methods to diagnose true ACS are needed.

The clinical investigators of this study (members of the Major Extremity Trauma and Rehabilitation Consortium) are currently undertaking a DOD-funded project to study the potential benefits of tissue ultrafiltration (TUF) in diagnosing and treating ACS (FY19 Defense Medical Research and Development Program (DMRDP) Restoring Warfighters with Neuromusculoskeletal Injuries Research (RESTORE) Award W81XWH2020050). One component of this RESTORE study is the evaluation of the diagnostic utility of serial samples of serum and ultrafiltrate biomarkers, including pH. However, continuous measurement of intramuscular pH is now available and has shown promise in the early diagnosis of ACS. The proposed study is a prospective observational pilot study of continuous intramuscular pH measurement in patients with severe lower leg injuries participating in the METRC RESTORE study.

The goal of the proposed project is to demonstrate that continuous measurement of tissue pH will show early and worsening abnormalities in the injured limb, to correlate those data with pressure monitoring data collected for the parent RESTORE study, and to compare tissue pH in patients receiving TUF versus standard of care. The data produced in this study will be used to inform the planning of a definitive study demonstrating the efficacy of tissue pH monitoring in the diagnosis of ACS. The over-arching goal is to improve the diagnosis of ACS to lessen the possibility of missed ACS (false negative diagnoses) as well as unnecessary fasciotomy (false positive diagnoses).

**Keywords:** extremity trauma, acute compartment syndrome, fasciotomy, intracompartment pressure, continuous pH measurement.

## 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 12 subtasks as listed below, with their milestones and status regarding completion.

Subtask 1: Finalize protocol, data collection protocols, months 1-2. Status: completed.

Subtask 2: Program and pilot test REDCap, the web-based system used for electronic data capture in all METRC studies, months 1-2. Status: 50% complete. Redcap programming is in progress and the required data input is being finalized with the vendor.

Subtask 3: Develop SOPs for pH monitoring protocol, Months 3-4. Status: 50% complete. Finalizing with the vendor.

Subtask 4: Obtain initial IRB approval at JHU (location of the MCC) and HCM (PI site), Month 3. Status: Not started. We anticipate completion in Q4 or early Q5. Before proceeding with IRB submission, an FDA NSR determination is needed. This was requested during Y1 and received 10-6-23.

Subtask 5: Submit approved protocol to USAMRMC OHRO for review, Month 3. Status: not started, Anticipate submission near end of Q4 or early Q5.

Subtask 6: Distribute approved protocol and obtain IRB approval at all participating sites, months 3-4. Status: not started. Anticipate completing in Q6.

Subtask 7: USAMRMC Human Research Protections Office review and approval of site-specific IRB-approved human use documents, months 5-6. Status: not started, anticipate completion in Q6.

Subtask 8: Develop training materials for Research Coordinators on study procedures and data collection. Training materials will include web-based training sessions, written guidance documents posted to the METRC website and standard operating procedure templates, Months 1-3. Status: not started but will be part of planned training activities for the parent study, which will be rolled out in Q5.

Subtask 9: Train Research Coordinators on study procedures and data collection, Months 3-4. Status: not started. Training will occur when all the sites are closer to finalizing the regulatory procedures and are closer to start enrollment.

Subtask 10: Certify sites to begin screening and enrolling patients, months 5-7: Status: not started. This is one of the final steps before study enrollment starts. Now anticipated in Q6.

Subtask 11: Conduct study initiation calls to review study procedures prior to initiation of screening and enrollment activities, months 5-7: Status: not started. This is one of the final steps before study enrollment starts. Now anticipated in Q6.

Subtask 12: The parent study (DM1970740/W81XWH-20-2-0050) has received IRB approval, HRPO approval, and has successfully enrolled the first subject, months 4-6. Status: 99% completed. Parent study received approval from the Johns Hopkins sIRB at the beginning of Q3 (4-10-23) and was approved by HRPO 5-8-23. Materials were submitted to sites for local submission 5-12-23, and 1 of 4 sites are approved. The first patient will be enrolled in Q4.

Major Task 2: Enroll and Follow Patients, months 8-24. Status: Not started.

Major Task 3: Data Analysis, months 24-36. Status: No planned work in Y1.

• **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.*

Work during Y1 involved finalizing the study protocol, related SOP's, and the REDCap data capture system. This work is complete, except for some final programming tasks and harmonization of SOPs between the parent study and this project. A non-significant risk determination letter was requested from FDA to facilitate the IRB review process and preempt any regulatory pushback (received 10/6/23). A one-year NCE was requested and received 9-30-2023.

**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 period. (Year 2) is to initiate and complete the enrollment of the planned 40 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.*

Nothing to report.

- **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.*

This parent RESTORE study experienced delays. The parent study will begin enrolling patients in Q4, allowing this study to commence. A one-year NCE was requested and has been approved. Request to release period B funds, per this study award, will be made in Q4 to allow the study to proceed.

- **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, most 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 Y1 are therefore much lower than planned, 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:	<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>0.13</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>0.60</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>Clinical Research Manager</i>
Researcher Identifier (e.g. ORCID ID):	<i>0000-0001-5305-1774</i>
Nearest person month worked:	<i>0.66</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>Project Director</i>
Researcher Identifier (e.g. ORCID ID):	<i>N/A</i>
Nearest person month worked:	<i>1.06</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:**

None