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TITLE: Safety and Feasibility of Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma (EPR-CAT)

PRINCIPAL INVESTIGATOR: Dr. Samuel Tisherman

CONTRACTING ORGANIZATION: University of Maryland, Baltimore

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

During this fifth year of the project, we have remained on clinical hold because of concerns about the local blood supply due to the COVID-19 pandemic. The supply has now improved. In addition, the FDA raised concerns about whether or not the study meets the requirements for the Exception from Informed Consent for emergency research. Specifically, they were not convinced that EPR provides the potential for benefit for individual subjects based upon the current data, which includes only 6 EPR subjects and 5 controls. We have submitted written responses to their concerns and held two video conference calls with them to clarify the issues. We provided a comprehensive report of the background of the study, the clinical data, our response to the unexpected clotting issues, and our explanation for why we believe the study should continue. We also made 2 evidence-based changes to the protocol to improve the potential for benefit for the individual subjects. First, we will only cool to 18^{o}C. Second, we will administer whole blood as the last blood products when coming off cardiopulmonary bypass.

We have decided not to include Stroger Hospital of Cook County in the remainder of the trial given the complex issues noted above and the fact that we can only enroll another 4 EPR subjects and 5 controls.

15. SUBJECT TERMS
Trauma, hemorrhagic shock, cardiac arrest, cardiopulmonary resuscitation, hypothermia

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Cardiopulmonary resuscitation (CPR) can save victims of non-traumatic cardiac arrest (CA), e.g., ventricular fibrillation. During exsanguination CA from trauma, however, CPR, even with an emergency department (ED) thoracotomy and open chest CPR, results in unacceptably low survival rates (<5%). *Emergency Preservation and Resuscitation (EPR)* was developed to rapidly preserve the whole body during ischemia, using hypothermia, drugs, and fluids, to "buy time" for transport and resuscitative surgery. Laboratory research has only demonstrated efficacy with hypothermia. The purpose of this study is to test the feasibility of rapidly inducing profound hypothermia (10^{o}C) with an aortic flush in trauma victims that have suffered CA and failed standard resuscitative efforts to enable resuscitative surgery and delayed resuscitation with cardiopulmonary bypass. The primary outcome variable will be survival to hospital discharge with minimal neurologic dysfunction.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Trauma, hemorrhagic shock, cardiac arrest, cardiopulmonary resuscitation, hypothermia

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

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.

Specific Aims
1. Rapidly identify appropriate candidates for EPR
2. Initiate EPR and achieve goal temperature within 25 minutes of subject identification
3. Compare the rate of hospital discharge without major neurologic disability in the EPR group with the concurrent control group
4. Compare the rates of 28-day survival, 1-year neurologic functional outcome, and the development of multiple organ dysfunction in the EPR group with the concurrent control group
5. Document direct complications of the EPR technique

Major Task 1: Regulatory approvals
1. Local IRB approval of community consultation and public disclosure plan
2. Conduct community consultation/public disclosure
3. Local IRB Approval
4. US Army HRPO Approval

Major Task 2: Training
1. IACUC Approval
2. ACURO Approval
3. Complete animal training
4. Complete cadaver training

Major Task 3: Retrospective review of trauma registries

1. Review of patients who have undergone a resuscitative thoracotomy

Major Task 4: Enroll patients in first 2 cohorts

1. Develop specific logistics with involved disciplines
2. Assure that all necessary equipment is ready
3. Subject enrollment at Site 1
4. Subject enrollment at Site 2
5. Enroll 10 EPR subjects and 10 control subjects

Major Task 5: Revise protocol

1. Evaluate data from first cohorts of 10 EPR and 10 control subjects
2. Revise protocol based upon data from first cohorts
3. Obtain approvals for second set of cohorts from DSMB, FDA, IRBs, and US Army HRPO

Major Task 6: Enroll patients in second 2 cohorts

1. Enroll 10 EPR subjects and 10 control subjects
2. Evaluate data from second set of cohorts of 10 EPR and 10 control subjects

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.

Major Task 1: Regulatory approvals

All approvals have been completed at the University of Maryland and the John H. Stroger Hospital of Cook County. The subcontract with the John H. Stroger Hospital of Cook County (Hektoen Institute for Medical Research) as a second site is also complete.

Major Task 2: Training

Training has been completed at the University of Maryland, which has IACUC and ACURO approval. Animal and cadaver training for the team at Stroger Hospital will be completed at the University of Maryland, rather than at Stroger Hospital, after the issues with the FDA have been resolved.

1. IACUC Renewal: completed
2. ACURO Renewal: completed
3. Complete animal training: cancelled for Stroger Hospital
4. Complete cadaver training: cancelled for Stroger Hospital

Major Task 3: Retrospective review of trauma registries

1. Review of patients who have undergone a resuscitative thoracotomy: we are still analyzing this data for any correlations that my help guide recruitment. Overall, however, the survival rate, as noted in previous reviews, remains approximately 5%.

Major Task 4: Enroll patients in first 2 cohorts

Enrollment is on hold at the University of Maryland.

1. Develop specific logistics with involved disciplines: Discussions have been cancelled at Stroger Hospital
2. Assure that all necessary equipment is ready: Discussions have been cancelled at Stroger Hospital
3. Subject enrollment at Site 1: Enrollment has remained on hold because of COVID-19 related effects on the blood supply and the recent issues raised by the FDA.
4. Subject enrollment at Site 2: The decision was made not to enroll at Site 2.
5. Enroll 10 EPR subjects and 10 control subjects: in progress. We currently have 6 EPR subjects and 5 control subjects.

Major Task 5: Revise protocol

Pending completion of enrollment of the first cohort of 10 EPR and 10 control subjects.

1. Evaluate data from first cohort of 10 EPR and 10 control subjects
2. Revise protocol based upon data from first cohorts
3. Obtain approvals for second set of cohorts from DSMB, FDA, IRBs, and US Army HRPO

Major Task 6: Enroll patients in second 2 cohorts

1. Enroll 10 EPR subjects and 10 control subjects
2. Evaluate data from second cohorts of 10 EPR and 10 control subjects

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."

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 for this period. We are preparing for refresher training since the study has been on hold for so long. Training of the Stroger Hospital team members will not be performed.

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?
If this is the final report, state "Nothing to Report."

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

We will restart recruitment of subjects at the University of Maryland once we have retrained the team.

IACUC and ACURO renewal have been completed.

4. **IMPACT:** D*escribe 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.

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.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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.

The cause for low enrollment at the University of Maryland is unclear. We are continuing to review our trauma registry and screening procedures with the research staff to be sure we are not missing potential subjects. This will be difficult to assess given that we have been on hold for >2 years. Bringing on the John H. Stroger Hospital of Cook County as a second site might have helped with overall study enrollment. On the other hand, given the unanticipated adverse events and the scrutiny by the FDA, we have decided to hold off on adding Stroger Hospital for this initial feasibility study.

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

The study has remained on clinical hold. Consequently, we have minimized any expenditures.

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.

Significant changes in use or care of human subjects

There have been no changes to the care of human subjects or vertebrate animals.

IRB approval date: 14-May-2019

IACUC approval date: 05-Sept-2019

Maryland State Anatomy Board approval date: 08-Jun-2015.

USAMRMC Office of Research Protections cadaver approval: 16-Jul-2015 under Proposal Log Number 07152001, Award Number W81XWH-07-1-0682.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. **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).*

  1. Tisherman SA: Emergency preservation and resuscitation for cardiac arrest from trauma. Ann NY Acad Sci. 2022;1509(1):5-11.

  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.

The following website was developed for disseminating information about the study as part of the public disclosure process. There is currently no information regarding results on this site. https://www.umms.org/ummc/health-services/shock-trauma/news/body-cooling-study

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were 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. 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;*
  - *physical 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.

7. 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".

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	Samuel A. Tisherman, MD
Project Role:	Principal investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-3810-3729
Nearest person month worked:	2
Contribution to Project:	Manages all aspects of the study, including training, readiness for enrollment, data management and analysis, submission of regulatory documents, and coordination with all sites. Dr. Tisherman is the sponsor of the Investigation Device Exemption.

Name:	Thomas Scalea, MD
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Training of surgeons involved in the project. Revisions to the clinical protocol. Identification of clinical sites.

Name:	Leslie Sult, RN
Project Role:	Research coordinator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Assists with training. Assures that equipment is available and personnel are prepared for subject enrollment. Supervises data collection.

Name:	Faran Bokhari, MD
Project Role:	Site principal investigator at John H. Stroger Hospital of Cook County
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Manage all aspects of the study at Stroger Hospital, including team oversight, data management, and submission of regulatory documents.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: Stroger Hospital of Cook County Location of Organization: Chicago, IL Partner's contribution to the project: Collaboration as second site for conducting the study.

8. **SPECIAL REPORTING REQUIREMENTS**
   COLLABORATIVE AWARDS: *N/A*

9. **QUAD CHARTS:** *N/A*

10. **APPENDICES:** *N/A*