CONTRACT NUMBER: W81XWH-19-F-0539

TITLE: Prehospital Analgesia Intervention Trial (PAIN)

PRINCIPAL INVESTIGATOR: Jason Sperry

CONTRACTING ORGANIZATION: University of Pittsburgh
Pittsburgh, Pennsylvania 15213

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Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
PAIN is a proposed 4 year (3-year enrollment) multicenter, prehospital, randomized, double-blind, clinical trial comparing fentanyl versus sub-dissociative ketamine for mortality outcome differences, safety and analgesia in trauma patients with compensated shock.

Specific aims are to determine if, among prehospital trauma patients with compensated shock (Heart Rate (HR)>109 or Shock Index (SI)>0.9) and an indication for pain management, treatment with sub-dissociative IV ketamine as compared to IV fentanyl reduces mortality at 24 hours following admission, reduces the frequency of hemodynamic instability or respiratory depression associated with analgesia, decreases total prehospital exposure to opioids, 24-hour exposure to opioids, and anxiety/PTSD screen scores, improves the frequency of complications including opioid use / dependency, anxiety, and PTSD at 6 months, and improves arrival pain control as measured by numerical rating scale (NRS) and/or the critical care pain observation tool (CPOT).

15. SUBJECT TERMS
Trauma; Prehospital; Analgesia; Fentanyl; Sub-Dissociative Ketamine

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	12	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

PAIN is a proposed 4 year (3-year enrollment) multicenter, prehospital, randomized, double-blind, clinical trial comparing fentanyl versus sub-dissociative ketamine for mortality outcome differences, safety and analgesia in trauma patients with compensated shock.

The primary outcome for the trial will be 24-hour mortality among trauma patients with compensated shock following administration of the prehospital analgesia. Secondary outcomes will include incidence of adverse events (hypoxia, hypotension, and need for airway management) occurring in the prehospital environment, assessed after administration of the analgesic intervention. prehospital pain assessment (NRS, CPOT) following analgesia, trauma bay arrival pain score, number of analgesic doses necessary to reduce pain level to <5 or CPOT less than 2, total 24-hour opioid use, incidence of prehospital adverse events (allergic reactions, emergence, laryngospasm, dysphoria, pruritus, and nausea), anxiety/PTSD screening, hospital length of stay, survival to hospital discharge, ventilator free days, ICU free days and long-term opioid use (6-month). Trial will utilize prehospital agencies at six LITES Network sites and will enroll a total of 1,544 subjects.

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

Trauma; Prehospital; Analgesia; Fentanyl; Sub-Dissociative Ketamine

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.

The purpose of Task Order 0006 is to perform a prospective, interventional, randomized trial among prehospital trauma patients with compensated shock (HR>109 or SI>0.9) and an indication for pain management, comparing patient centered outcomes following prehospital administration of ketamine hydrochloride versus fentanyl citrate.

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.

- CCC submitted Pre-IND and requested Type B meeting with the FDA for guidance on protocol and IND development in 2019.
- Hired study Project Manager and Assistant Project Manager in NOV and DEC-2019 respectively.
- CCC identified criterion for study site selection and distributed two surveys of network sites to guide site selection. determining potential sites for consideration.
    - 11 potential sites have been identified.
- Study team identified a supplier and 503B outsourcing facility, Pine Pharmaceuticals, for compounding, packaging, and distribution of study drugs.
    - CCC conducted in-person meeting with Pine Pharmaceuticals to clarify compounding process and study product.
- CCC finalized and submitted IND application to FDA on 20-MAR-2020 and received Full Clinical Hold on 27-APR-2020.
    - CCC conducted informational calls with FDA Ombudsman and FDA CDER Formal Dispute Resolution Project Manager to determine course of action for responding to Clinical Hold. Followed FDA guidance to formally request a Type A meeting.
    - CCC conducted Type A Meeting with FDA on 15-JUL-2020; received official FDA minutes from Type A meeting on 13-AUG-2020.
    - Submitted response to FDA Clinical Hold on 02-SEP-2020 and anticipate FDA response in OCT-2020.

Enrollment: not yet recruiting.

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."

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."

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.

- Obtain FDA/IND approval and approval to conduct study under EFIC.
- Submit and obtain IRB approval.
- Finalize site selection and begin local IRB community consultation/public disclosure planning and site budgets.
- Continue ongoing communications with Pine Pharmaceuticals.

Travel Reporting: no travel is anticipated for the next quarter (OCT-2020 to DEC-2020).

Cumulative to Billing Period: 30-SEP-2020	Travel Funds Budgeted	Cumulative Actual Spent	Remaining Balance
	$212,365.42	$730.52	$211,634.90
Upcoming Travel for Quarter: **SEP-2020 to DEC-2020**	Traveler Name	Destination/ Purpose	Estimated Date of Travel
1			
Travel for Quarter: **JAN-2020 TO MAR-2020**	Traveler Name	Destination/ Purpose	Estimated Date of Travel
1	Susana Traub	Tonawanda, NY	11-MAR to 12-MAR 2020
2	Pete Adams	Tonawanda, NY	11-MAR to 12-MAR 2020
3	Ashley Harner	Tonawanda, NY	11-MAR to 12-MAR 2020
4	Natalie Rogers	Tonawanda, NY	11-MAR to 12-MAR 2020

4. 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.

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.

- Ongoing communication with FDA about conducting the study under EFIC (Exception from Informed Consent).
- CCC/DCC are working together to anticipate and respond to unique obstacles that may result from site/EMS agency priorities shifting to COVID-19 pandemic response.

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.

Nothing to Report

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

Nothing to Report

Significant changes in use or care of vertebrate animals

Not applicable to TO 0006

Significant changes in use of biohazards and/or select agents

Not applicable to TO 0006

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).*

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. 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.)*

Personnel Listing: see page 12

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.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

Quad Chart: see page 12

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Annual and final reports are submitted to: https://ers.amedd.army.mil/

AND
One Copy: Contract Specialist, Mr. Paul Martha
Email: paul.m.martha.civ@mail.mil

One e-Copy: Science Officer René Smith
Email: rene.k.smith.civ@mail.mil

Personnel Listing (as of 05-OCT-2020)

Department	Last Name	First Name	Government Used Labor Category	UPitt Role	PAIN/6
Surgery	Brown	Joshua	Clinical Research Director	CO-Investigator	2.5%
Epidemiology (GSPH)	Wisniewski	Stephen	Epidemologist	Co-PI	5%
Emergency Medicine	Pacella	Maria	Clinical Research Director	CO-Investigator	5%
Epidemiology (GSPH)	Silfies	Laurie	Systems Engineer IV	Systems Engineer IV	20%
Emergency Medicine	Guyette	Francis	Clinical Research Director	Co-PI	25%
Surgery	Sperry	Jason	Clinical Research Director	PI	25%
Epidemiology (GSPH)	Kania	Michael	Systems Developer III	Systems Developer III	50%
Epidemiology (GSPH)	Macey-Kalcevic	Melody	Database Adminstration Manager (TBD Data Aanalyst R IV)	Research IV	50%
Surgery	Rodgers	Natalie	Clinical Research Coordinator (Research Coordinator R III)	Research Coordinator (CRC)	100%

YEAR 1 QUAD CHART

Linking Investigations in Trauma and Emergency Services – TO6

17052001-TO6/W81XWH-16-D-0024, W81XWH19F0539

Prehospital Analgesia Interventional (PAIN) Trial - LITES Task Order 0006

PI: Jason Sperry MD MPH **Org:** University of Pittsburgh **Award Amount: $8,798,845.00**

STUDY AIMS

Determine if prehospital management of moderate to severe pain with sub-dissociative IV ketamine as compared to IV fentanyl in patients at risk of hemorrhage or compensated shock:

I. Reduces 24-hour mortality
II. Improves the incidence of hemodynamic instability or respiratory depression (hypotension, hypoxia or need for airway management) following analgesia for traumatic injury
III. Decreases total prehospital exposure to opioids, 24-hour exposure to opioids, and Anxiety/PTSD screen scores
IV. Improves the frequency complications including opioid use/ dependency, anxiety, and PTSD at 6 months
V. Improves pain control as measured by NRS or CPOT scores in patients at risk of hemorrhage or compensated shock

APPROACH

Multicenter, prehospital, randomized, double-blind, clinical trial

Comparing fentanyl versus sub-dissociative ketamine for mortality outcome differences, analgesia and safety in trauma patients at risk of hemorrhage or compensated shock.

ACCOMPLISHMENTS

- ✓ CCC conducted Type A meeting with FDA and responded to Full Clinical Hold in SEP-2020.
- ✓ Continued ongoing communication with Pine Pharmaceuticals (FDA-registered 503B outsourcing facility)

Timeline and Cost

Activities / CY	19	20	21	22
Startup, Hiring, IRB approval, Contracts, Central IRB organization, Database creation, site selection				
4-year (3-year enrollment), 1544 patients (772 per group)				
1/3 enrollment; interim analysis				
2/3 enrollment; interim analysis				
Estimated Budget ($K)	**$2.2M**	**$2.2M**	**$2.2M**	**$2.2M**

Updated: (University of Pittsburgh 06-OCT-2020)

Goals/Milestones

CY19 Goal – Study Development & Staffing
- ✓ Base Hiring
- ✓ Budget negotiation

CY20 Goal – Study Startup & Site Selection Community consultation and public disclosure
- ❑ FDA IND, Central IRB approval
- ❑ Site selection

CY21 Goal – Patient enrollment
- ❑ Data base creation and CRF completion, data dictionary
- ❑ Site Initiation Visits
- ❑ Begin Patient enrollment
- ❑ Reach accrual goal for 1/3 interim analysis
- ❑ Enrollment
- ❑ Reach accrual goal for 2/3 interim analysis

CY22 Goal – Patient Enrollment
- ❑ Finish enrollment
- ❑ Data analysis and publication

Comments/Challenges/Issues/Concerns
- Ongoing communication with FDA about conducting the study under EFIC (Exception from Informed Consent).
- Anticipating unique challenges presented by site/EMS agency priorities in response to COVID-19

Budget Expenditure to Date
- Actual Expenditures To-Date: **$340,337.65** (reflected level reports up to 31-AUG-20)
- Projected Expenditures: $32,675 *(reflects current projections on account for AUG20 period).*