

**CONTRACT NUMBER:** W81XWH-19-F-0539

**TITLE:** Prehospital Analgesia Intervention Trial (PAIN)

**PRINCIPAL INVESTIGATOR:** Dr. Jason Sperry

**CONTRACTING ORGANIZATION:** University of Pittsburgh

**REPORT DATE:** October 2021

**TYPE OF REPORT:** Annual – Year 2

**PREPARED FOR:** U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

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# REPORT DOCUMENTATION PAGE

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<b>1. REPORT DATE</b> October 2021			<b>2. REPORT TYPE</b> Annual Report		<b>3. DATES COVERED</b> 20-SEP-2020 to 19-SEP-2021	
<b>4. TITLE AND SUBTITLE</b>  Prehospital Analgesia Intervention Trial (PAIN)					<b>5a. CONTRACT NUMBER</b>	
					<b>5b. GRANT NUMBER</b> W81XWH-19-F-0539	
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<b>6. AUTHOR(S)</b>  Jason L. Sperry, Barbara Early, Meghan Buck, Laurie Silfies, Natalie Rogers  E-Mail: <a href="mailto:sperryjl@upmc.edu">sperryjl@upmc.edu</a> ; <a href="mailto:earlybj@upmc.edu">earlybj@upmc.edu</a> ; <a href="mailto:buckml@upmc.edu">buckml@upmc.edu</a> ; <a href="mailto:silfiesl@edc.pitt.edu">silfiesl@edc.pitt.edu</a> ; <a href="mailto:rogersnb@upmc.edu">rogersnb@upmc.edu</a>					<b>5d. PROJECT NUMBER</b>	
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<b>13. SUPPLEMENTARY NOTES</b>						
<b>14. ABSTRACT</b> 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).						
<b>15. SUBJECT TERMS</b> Trauma; Prehospital; Analgesia; Fentanyl; Sub-Dissociative Ketamine						
<b>16. SECURITY CLASSIFICATION OF:</b>				<b>17. LIMITATION OF ABSTRACT</b>  Unclassified	<b>18. NUMBER OF PAGES</b>  12	<b>19a. NAME OF RESPONSIBLE PERSON</b> USAMRMC
<b>a. REPORT</b>  Unclassified	<b>b. ABSTRACT</b>  Unclassified	<b>c. THIS PAGE</b>  Unclassified	<b>19b. TELEPHONE NUMBER (include area code)</b>			

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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

- Successful virtual In Progress Review (IPR) meeting held on 01-DEC-2020!
- CCC is having ongoing communication with the University of Washington (Seattle) to join the LITES Network with the possibility of participating in PAIN as an enrolling site (ground EMS); anticipating a decision in OCT-2021.

## Sites

- CCC working to select participating sites (6 sites + Pittsburgh).
  - 8 potential sites were identified for site feasibility inquiry distributed in FEB-2021.
  - All potential sites responded by the end of JUN-2021 and investigators are ranking potential sites based on feasibility responses.

## FDA

- CCC received FDA Continue Clinical Hold letter 02-OCT-2020 and conducted informational call with FDA Assistant CDER Ombudsman to determine next steps on 14-OCT-2020.
- CCC submitted response to FDA Clinical Hold to FDA Gateway 17-NOV-2020 and continuation of Clinical Hold confirmed via teleconference 11-DEC-2020; official advice letter received in JAN-2021.
- Investigators & CCC drafted responses to hold and non-hold comments to accompany stability testing results in response to FDA Full Clinical Hold; stability test results anticipated to be delivered in NOV-2021.
  - Response to FDA Full Clinical Hold is anticipated for Q4 2021 (pending receipt of 30-day stability testing results from Pine Pharmaceuticals estimated to be completed 25-OCT-2021).

## Pine Pharmaceuticals

- CCC maintaining ongoing communication with Pine Pharmaceuticals (FDA-registered 503B outsourcing facility).
  - CCC working with Pine to finalize subcontract agreement.
  - CCC conducted teleconferences with Pine Pharmaceuticals throughout this reporting period (15-DEC-2020, 01-JUN-2021, 08-JUL-2021, 02-SEP-2021) to initiate stability testing, review ongoing state registration for controlled distribution, design study drug packaging, and discuss Scope of Work, budget, logistics & timelines.
  - Validation testing in progress (stability testing to 90-day to follow; 30-day for FDA response)
  - PAIN Study Drug Testing Timeline (per contract lab estimates): *see table below*

Validation work to be completed & documentation issued to Pine for review/approval.	Week of 13-SEP-2021
Manufacture and ship stability batches to contract laboratory.	Week of 20-SEP-2021
T = 0 testing initiates at contract laboratory	Week of 27-SEP-2021
First results from T = 30 time point if desired	Week of 25-OCT-2021
<i>Results will be available 1-2 weeks after 30-day test is completed</i>	Week of 01-NOV-2021
First results from T = 45 timepoint	Week of 08-NOV-2021
T = 90-day results	Week of 02-DEC-2021
Target to commence enrollment Q2 2022 (will be adjusted as needed – pending FDA approval, site selection, IRB approval, SECARMY signature, HRPO approval, eDCF build).	

**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.*

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

**Travel Reporting:** no travel is anticipated for the next quarter (OCT-2021 to DEC-2021).

<b>Cumulative to Billing Period: 30-SEP-2021</b>	<b>Travel Funds Budgeted</b>	<b>Cumulative Actual Spent</b>	<b>Remaining Balance</b>
	\$212,365.42	\$730.52	\$211,634.90
<b>Upcoming Travel for Quarter: OCT-2021 to DEC-2021</b>	<b>Traveler Name</b>	<b>Destination/ Purpose</b>	<b>Estimated Date of Travel</b>
	N/A	N/A	N/A

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.
- Pine Pharmaceuticals has implemented a new program which has caused delays in finalizing Scope of Work and budget.

**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](mailto:paul.m.martha.civ@mail.mil)

One e-Copy: Science Officer René Smith

Email: [rene.k.smith.civ@mail.mil](mailto:rene.k.smith.civ@mail.mil)

### Personnel Listing (as of 31-AUG-2021)


Department	Personnel Name	Government Used Labor Category	UPitt Role	TO % Effort
Surgery	Brown, Joshua B	Clinical Research Director	Co-PI	3%
Emergency Medicine	Guyette, Francis X III	Clinical Research Director	Co-PI	11%
Surgery	Hayes, Hannah E	Clinical Researcher II	Clinical Researcher II	10%
Epidemiology (GSPH)	Kania, Michael A	Systems Developer III	Systems Developer III	50%
Emergency Medicine	Pacella, Maria Lynn	Clinical Research Director	CO-Investigator	5%
Epidemiology (GSPH)	Pattison, Angela Dawn	Database Administrator III	Research IV	63%
Surgery	Rogers, Natalie	Clinical Research Coordinator (Research Coordinator)	Research Coordinator (CRC)	50%
Epidemiology (GSPH)	Silfies, Laurie N	Systems Engineer IV	Systems Engineer IV	20%
Surgery	Sperry, Jason L	Clinical Research Director	PI	25%
Epidemiology (GSPH)	Wisniewski, Stephen R	Epidemiologist	Co-PI	5%

### YEAR 2 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**





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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

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


➔


ACCOMPLISHMENTS

- ✓ Continued collaborating with Pine Pharmaceuticals (FDA-registered 503B outsourcing facility) to ensure stability testing initiated.
- ✓ Validation testing in progress (stability testing to 90-day to follow; 30-day for FDA response)

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Timeline and Cost

Activities	CY	SEP-19	20	21	22	23
Startup, Hiring, IRB approval, Contracts, Single 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		252K	252K	252K	4M	4M

Goals/Milestones

**CY19 | CY20 Goal – Study Development & Staffing**

- ✓ Base Hiring & Budget negotiation

**CY21 | CY22 Goal – Study Startup, Site Selection, Community Consultation/Public Disclosure**

- Site selection
- FDA IND, single IRB approval
- Data base creation and CRF completion, data dictionary
- SecArmy EFIC waiver approval
- Site Initiation Visits
- HRPO approval
- Begin Patient enrollment
- Reach accrual goal for 1/3 interim analysis

**CY23 Goal – Patient Enrollment**

- Request No Cost Extension (NCE)
- Reach accrual goal for 2/3 interim analysis
- Finish enrollment
- Data analysis and publication

**Comments/Challenges/Issues/Concerns**

- Ongoing communication with FDA about conducting the study under EFIC.
- Anticipating unique challenges presented by site/EMS agency priorities in response to COVID-19.
- Pine Pharmaceuticals implemented a new program which has caused delays in finalizing Scope of Work and budget.

**Budget Expenditure to Date**

- Actual Expenditures To-Date: \$757,211 (reflected level reports up to 31-AUG-2021)
- Current Month Expenses: \$34,119 (reflects account through AUG-31 period)

**Updated:** (University of Pittsburgh 06-OCT-2021)