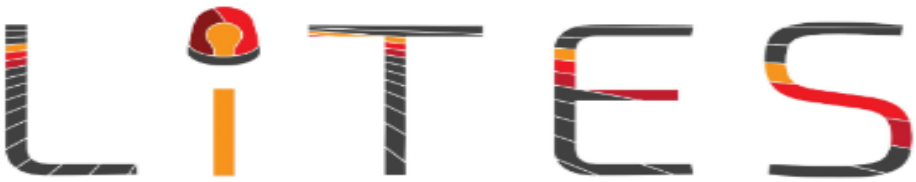


Linking Investigations in Trauma and Emergency Services

Task Order 0008

DSUVIA Early Evaluation of Pain (DEEP) Trial

Protocol v3 1.12.2023

Contents

Protocol Synopsis

Protocol Title:	DSUVIA Early Evaluation of Pain (DEEP) Trial
Protocol Number:	STUDY21100180
NCT Number:	NCT05288348
Version # and Date:	Version 3 1/12/2023
Investigational Drug:	DSUVIA as compared to standard care pain treatment
Trial Sites:	Clinical Coordinating Center • University of Pittsburgh, University of Pittsburgh Medical Center, Co-PI Jason Sperry, Co-PI Frank Guyette Additional Sites: • TBD
Funding Agency	Department of Defense
Study Aims:	Objectives for the study aims: (1) To conduct a prospective, randomized, interventional trial to examine effectiveness, safety, and acceptability of DSUVIA compared to standard care pain treatment in an emergency department (ED) setting in patients following traumatic injury with moderate to severe pain. (2) To analyze pain treatment effectiveness outcomes including: a. Verbally administered Numeric Rating Scale (VNRS) for clinical pain measurement (0-100) 30 minutes after pain medication administration b. Adverse effects and events related to pain medication(s) including nausea/vomiting, headache, dizziness, hypoxia, hypotension, and need for advanced airway c. Verbally administered Numeric Rating Scale (VNRS) for clinical pain measurement (0-100) at 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration d. Patient Global Assessment (PGA) of Pain Control at 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration e. Richmond Agitation-Sedation Scale score at 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration f. Time-weighted summed pain intensity difference (SPID) at 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration

	g. Number of rescue doses of narcotic at 30 minutes and during ED stay (up to 120 minutes) h. Time to reduction of NRS pain score of 10 points i. Cognitive function assessment with the Six Item Screener (SIS) at 30 minutes j. Healthcare Professional Global Assessment (HPGA) of the Method of Pain Control at 30 minutes k. Acceptability to health care providers survey
Study Design:	Prospective, randomized, interventional trial
Planned Sample Size:	N= 150 total; 75 each arm
Planned Study Duration:	3 years
Major Inclusion Criteria:	**1.** Trauma activation (Level I, II or III) **2.** Age 18 years to 70 inclusive. **3.** Blunt or penetrating injury **4.** Need for pain treatment based upon an VNRS clinical pain measurement ≥ 50 **5.** Estimated time in Emergency Department > 30 minutes following informed consent
Major Exclusion Criteria:	**1.** Advanced airway management prior to 1st dose administration **2.** Known allergy to fentanyl, sufentanil, or meperidine **3.** Known prisoner **4.** Known pregnancy **5.** ED pain treatment contraindicated per standard care **6.** Estimated BMI >40 **7.** Significant respiratory depression **8.** Known or suspected gastrointestinal obstruction, including paralytic ileus
Primary Outcome:	Verbally administered Numeric Rating Scale (VNRS) for clinical pain measurement (0-100) at 30 minutes following randomized medication administration

I. Objective and Specific Aims

Our objective is to perform a prospective, randomized, interventional trial of Emergency Department (ED) administration of DSUVIA versus standard care pain management comparing pain treatment outcomes in injured patients with moderate to severe pain.

AIM #1: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED reduces the Verbally administered Numeric Rating Scale (VNRS) for clinical pain measurement (0-100) at 30 minutes.

Hypothesis #1: Null Hypothesis: There will be no difference in the pain score at 30 minutes of patients who received DSUVIA as compared to standard care pain medicine in trauma patients

AIM #2: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED reduces adverse effects and events related to pain medication(s) including nausea/vomiting, headache, dizziness, hypoxia, hypotension, and need for advanced airway.

Hypothesis #2: Null Hypothesis: There will be no difference in the rate of adverse events of nausea/vomiting, headache, dizziness, hypoxia, hypotension and need for advanced airway in patients who received DSUVIA as compared to standard care pain medicine in trauma patients.

AIM #3: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED improves pain treatment effectiveness including serial VNRS scores (every 30 minutes), the need for rescue narcotic administration, the time needed to reduce the VNRS pain score by 10 points, time-weighted summed pain intensity difference, patient global assessment (PGA), Six Item Screener (SIS) cognitive assessment and Richmond Agitation-Sedation Scale scores.

Hypothesis #3: Null Hypothesis: There will be no difference in the pain treatment effectiveness, need for rescue narcotic administration, time to reduction of 10 points of VNRS pain score by 10 points, the time-weighted summed pain intensity difference, patient global assessment, Six-Item Screener and the Richmond Agitation-Sedation Scale scores in patients who received DSUVIA as compared to standard care pain medicine in trauma patients.

AIM #4: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED improves Healthcare Professional Global Assessment (HPGA) of the Method of Pain Control and health care provider survey scores.

Hypothesis #4: Null hypothesis: There will be no difference in the Healthcare Professional Global Assessment (HGPA) of the method of pain control and healthcare provider survey scores in patients who received DSUVIA compared to standard care pain medication in trauma patients.

II. Background and Significance

The management of pain following an acute injury is an essential part of caring for a trauma victim in both the military and civilian systems.[1] Providing analgesia as soon as practicable is humane, reduces suffering, moderates physiologic complications of trauma, and may mitigate the incidence of long-term sequelae such as chronic pain and PTSD.[2,3] Reviews of pain management demonstrate high variability and inconsistency in the reporting, assessment, and treatment of pain.[4,5] Pain management is further complicated by fears and misconceptions of adverse events, chemical dependency, and implicit bias.[6] Current prehospital pain management strategies rely on parenteral medications to provide rapid relief because oral medications are slow in onset and absorption from intramuscular injections is unpredictable.[7] In combat, only 7% of casualties had a pain score recorded and only 15% received any analgesic.[5] In less austere environments, providers only assess pain in 2/3 of patients. Pain following traumatic injury is common (81%), severe (73%), infrequently treated (47%), and the management inadequate (25%).[8]

Guidelines from the National Association of EMS Physicians (NAEMSP) recommend assessing pain in all patients, using a self-reported pain score (NRS), using opioid analgesics (morphine or fentanyl), reassessing pain and adverse effects frequently, and redosing analgesia if significant pain remains.[4] Greater granularity in pain assessment is achieved with a verbally administered NRS which has been extensively applied in ED settings during the assessment of acute pain.[9-11]

The NAEMSP guidelines focus on intravenous (IV) fentanyl and morphine because of wide availability among American EMS services. Use of IV opioids is limited by the need to obtain IV access, which can be time consuming, is associated with a significant failure rate, and may lead to increased exposure in a tactical environment.[12] The US military uses oral transmucosal fentanyl citrate (OTFC) which can be administered without IV access, but has slow absorption. Furthermore, safety data on OTFC, outside of long-term analgesia for cancer patients, is not well described.[7] Given these significant limitations, an alternative to IV opioid analgesics in necessary. The ideal agent has robust stability, easy delivery, rapid onset, minimizes altered mental status and has a wide therapeutic index.[13] In addition, the ideal agent would have a longer duration of action and an improved side effect profile as compared to the current standard care.

Sufentanil is a potent opioid analgesic derived from fentanyl with no active metabolites, rapid onset, and a therapeutic index superior to morphine and fentanyl.[14] Sufentanil is highly lipophilic and rapidly achieves equilibrium in the brain; the time to analgesia is similar to IV morphine.[15] When administered sublingually, sufentanil is 53% of the IV bioavailability within one minute and provides analgesia within 15 minutes.[15,16] Sufentanil has a low incidence of side effects, with nausea, headache, dizziness, and vomiting being the most common.[15] As with any opioid, respiratory depression and hypoxia can occur but was observed to be <1%.[17] Similar studies found no clinically significant changes in vital signs after the administration of sublingual sufentanil in post-operative patients.[18,19] Sufentanil was effective in a cohort of patients with painful injuries presenting to the ED with pain reduction seen in less than 15 minutes and persisting for 2 hours.[17]

These data suggest that in this cohort of injured patients with moderate to severe pain, sublingual sufentanil (DSUVIA) may provide similar analgesia to IV opioids. Similar to standard care with IV fentanyl or morphine, sufentanil (DSUVIA) is effective, rapid in onset, and has a favorable side effect profile. DSUVIA has the advantage of sublingual administration, precluding the need for IV access while providing rapid analgesia. In addition, sublingual administration of sufentanil provides longer duration of analgesia compared to IV fentanyl and more rapid absorption and analgesia then OTFC. The current management of pain in this injured cohort is inadequate and demonstrates the need to determine the efficacy and safety of DSUVIA (sublingual sufentanil) as compared to standard care for pain management in the prehospital setting.

III. Study Design/Setting

The current proposed study will be a 3-year, multi-center, open label, randomized trial utilizing 2-4 level-1 trauma centers from within the LITES network and will enroll approximately 150 patients. The University of Pittsburgh will be the Clinical Coordinating Center and the Data Coordinating Center for the study.

Study Population:

Blunt or penetrating injured patients who require pain management in the Emergency Department phase of care.

Inclusion Criteria

1. Trauma activation (Level I, II or III)
2. Age 18-70 years inclusive.
3. Need for pain treatment based upon an NRS (0-100) clinical pain measurement ≥ 50
4. Estimated time in Emergency Department > 30 minutes following informed consent

Exclusion Criteria

1. Advanced airway management prior to 1st dose administration

2. Known allergy to fentanyl, sufentanil, or meperidine
3. Known prisoner
4. Known pregnancy
5. ED pain treatment contraindicated
6. Estimated BMI >40
7. Significant respiratory depression
8. Known or suspected gastrointestinal obstruction, including paralytic ileus

Study Intervention: The study intervention will be the administration of 30 micrograms of DSUVIA in tablet form utilizing a sublingual applicator following informed consent for participation.

Study Intervention Arm**:** Patients randomized to the study intervention arm will receive DSUVIA via approved applicator as soon as feasible after randomization. A single dose of DSUVIA will be provided as directed on the package insert. Pre-randomization pain treatment will not be prohibited for study participation and dosage and narcotic type will be documented and recorded.

Standard Care Arm**:** Patients randomized to the standard care arm will receive standard care pain management. Dose administered and the respective narcotic will be recorded. Pre-randomization pain treatment will not be prohibited for study participation and dosage and narcotic type will be documented and recorded.

Randomization and Masking: Individual patients meeting all inclusion and no exclusion criteria in the emergency department will be randomized and assigned according to a 1:1 ratio of DSUVIA or standard care pain treatment using a permuted block design with variable block sizes of 4 and 6. A predefined randomization assignment will be utilized. The arm assignment will be provided in real time at the individual patient level. Trauma attending and ED physicians will not be masked to treatment assignment as the study intervention will not be blinded. Arm assignment will be concealed to all outcome assessors for follow up.

IV. Outcomes

Primary Outcome**:** The primary outcome for the pilot trial will be the Verbally administered Numeric Rating Scale (VNRS) for clinical pain measurement (0-100) at 30 minutes following randomized medication administration. [9-11]

Secondary Outcomes**:** Secondary outcomes will include adverse events including hypoxia needing supplemental oxygen (SpO2 < 90%); hypotension (systolic blood pressure < 90mmHg); advanced airway or bag mask ventilation; incidence of nausea/vomiting/headache/dizziness requiring treatment; serial (30 minute intervals until ED discharge, up to 120 minutes or rescue narcotic administration) measurements of a) VNRS for clinical pain (0-100), b) Patient Global Assessment (PGA) of Pain Control**,** c) Richmond Agitation-Sedation Scale (RASS) scores, and d) time-weighted Summed Pain Intensity Difference (SPID); number of rescue narcotic doses at 30 minutes and during ED stay (up to 120 minutes); time to a reduction in VNRS pain score of 10 points; patient cognitive function as assessed by the Six Item Screener (SIS) at 30 minutes; Healthcare Professional Global Assessment (HPGA) of the method of pain control at 30 minutes; and acceptability of pain treatment to health care providers.

Secondary Outcome Definitions:

Hypoxia, hypotension or need for advanced airway: The principal safety outcome for the trial will be the incidence of serious adverse events following the first dose of analgesic following randomization including hypoxia (SpO2 < 90%), hypotension (SBP < 90 mmHg) or the need for advanced airway management (placement of an endotracheal tube, supraglottic airway or bag mask ventilation) until ED discharge (up to 120 minutes), when feasible.

Composite outcome of nausea, vomiting, headache, and/or dizziness requiring treatment: The incidence of nausea, vomiting, headache, and/or dizziness requiring treatment will be recorded for initial 30 minutes, when feasible.

Verbally administered Numeric Rating Scale (VNRS) pain measurements (0-100) at 30-minute intervals: VNRS for clinical pain (0-100) measurements at approximate 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration, will be obtained when feasible.

Patient Global Assessment (PGA) of Pain Control at 30-minute intervals: The PGA of the method of pain control at approximate 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration, will be obtained when feasible. The research team will read the following statement aloud to the subject and the response will be recorded: "Overall, would you rate this method of pain control during the last 30 minutes/hours as being poor (1), fair (2), good (3), or excellent (4)?[20]"

Richmond Agitation-Sedation Scale (RASS) score at 30-minute intervals:
A RASS score at approximate 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration, will be obtained when feasible. (-5 to 4+; 10-point scale).[21]

Time-weighted Summed Pain Intensity Difference (SPID) at 30-minute intervals:
Time-weighted SPID measurements will be calculated at approximate 30-minute intervals until discharge from the ED (up to 120 minutes) or rescue narcotic administration, will be determined when feasible.[22] Essentially, the SPID represents serial assessments of pain intensity over time, weighted by time differences. SPID will be calculated using values from a 101-point continuous pain intensity scale (0 = no pain to 100= worst pain imaginable). The Pain Intensity Difference (PID) (e.g., raw differences in pain intensity) is calculated by subtracting the pain intensity at each time point from the pain intensity at time 0. The SPID is then calculated by multiplying the PID score at each post dose time point by the duration (in hours) since the preceding time point and then summing the values over the relevant time period.[11] If patients did not complete the full 120 minutes, the last pain observation was carried forward.[23]

Number of rescue doses of narcotic at 30 minutes and until ED discharge (up to 120 minutes): The number of doses of standard care pain treatment given within 30 minutes following randomly assigned intervention and total until ED discharge (up to 120 minutes), when feasible.

Time to reduction of VNRS pain score of 10 points (up to 120 minutes)
The time in minutes will be determined for the VNRS pain score (0-100) to be reduced by 10 points following randomized assignment administration for patients, when feasible.

Cognitive function at 30 minutes using Six Item Screener (SIS): The SIS[24] will be used to detect cognitive impairment (e.g., sleepiness, confusion, memory impairment and reaction time)

at 30 minutes. Using a cutoff of ≤ 4 (out of 6) to reflect cognitive impairment has been proposed for ED use[25] and has been used in prior studies of treatment of acute pain with sufentanil in the ED.[22]

Healthcare Professional Global Assessment (HPGA) of the Method of Pain Control at 30 minutes: The HPGA of the method of pain control will also be reported by the healthcare professional (primarily nurses) at the 30-minute time period as the PGA above.[26]

Acceptability to health care providers survey: An acceptability to health care providers score will be requested of health care providers in the ED including ED nurse, ED trauma team member and/or trauma surgery team member at 30 minutes or when feasible. The score (-2 to +2; 5-point scale) ratings will be from; very dissatisfied, dissatisfied, neither satisfied nor dissatisfied, satisfied, very satisfied, and will document providers assessment regarding the individual patient's pain management process, ease and acceptability relative to past experiences, when feasible.

Predefined Subgroups**:** Predefined subset analyses will be performed on: sex (male/female), Injury Severity Score (ISS < or ≥ 16), age (< or ≥ 50), blunt versus penetrating injury, history of pre-injury opioid use (Y/N), air versus ground prehospital transport, transport origin (scene versus outside ED).

V. Screening and Enrollment

Subjects will be identified prospectively in the ED by research personnel that are trained and familiar with the inclusion and exclusion criteria. Those patients who meet all inclusion and no exclusion criteria will be approached for informed consent, and once obtained, randomized to DSUVIA or standard care based upon the predetermined randomization assignment. Subjects will be paid $25.00 in a Vincent Pay card upon completion of the study.

VI. Statistical Analysis Plan

Random Assignment: Participants will be randomly assigned in a 1:1 ratio to either DSUVIA or standard of care, stratified by site. Within each stratum, random assignment will be blocked, with random block size of two and four.

Analyses: All analyses will be carried out based on the intention-to-treat principle. Of those randomly assigned, the analyses will begin by describing the overall characteristics of the study population at the time of random assignment. Baseline characteristics will be described overall using summary statistics (e.g., means, standard deviation, percentages) and graphical techniques (e.g., histograms, box plots). Baseline characteristics between the two groups will be compared using t-tests or Wilcoxon tests for continuous variables and a chi-square tests for discrete variables.

The analyses for each aim are presented below.

AIM #1: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED reduces the Verbally Administered Numeric Rating Scale (VNRS) for clinical pain measurement (0-100) at 30 minutes.

A t-test will be used to compare the mean VNRS scores between the two treatment groups. A multivariable regression model will be used to compare the means after adjusting for stratification

variables (i.e., site) and baseline characteristics not balanced through random assignment. All assumptions of the analyses will be tested (e.g., normality of residuals). If any assumptions are violated, transformations of the data will be investigated and the transformed data will be analyzed and evaluated. If an adequate transformation cannot be identified, nonparametric methods will be used.

AIM #2: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED reduces adverse effects and events related to pain medication(s) including nausea/vomiting, headache, dizziness, hypoxia, hypotension, and need for advanced airway.

The adverse events will be analyzed in composite (any of them) and individually. For each, a chi-square test will be to compare the proportion of events between the two treatment groups. A multivariable logistic regression model will be used to compare the proportions after adjusting for stratification variables (i.e., site) and baseline characteristics not balanced through random assignment

AIM #3: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED improves pain treatment effectiveness including serial VNRS scores (every 30 minutes), the need for rescue narcotic administration, the time needed reduce the VNRS pain score by 10 points, time-weighted Summed Pain Intensity Difference, Patient Global Assessment (PGA), Six Item Screener (SIS) cognitive assessment, and Richmond Agitation-Sedation Scale scores.

The analysis plan will vary based on the time of outcome variable. For binary outcomes (e.g., need for rescue narcotic administration), analyses identical to those described for Aim 2 will be carried out. For longitudinal data with repeated measures (e.g., VNRS scores every 30 minutes), a mixed-effect regression model will be used to compare the average scores over time. Main effects will include an indicator of treatment group, site, and baseline characteristics not balanced through random assignment. Random effect will include intercept and slope. For time to event analyses (e.g., time to reduce VNRS pain by 10 points, a Kaplan-Meier curve will be used to describe the distribution of time to event between the two treatment groups and a Log-Rank test will be used to test for differences between the two curves. A Cox Proportional-hazards model will be used to compare the distribution, after controlling for site and baseline characteristics not balanced through random assignment. For ordinal discrete outcomes (e.g., RASS), a Wilcoxon test will be use do compare scores between the two treatment groups. A nonparametric regression approach will then be used to examine for differences between the two treatment groups after adjusting for site and baseline characteristics not balanced through random assignment.

AIM #4: To determine if, among injured patients with moderate to severe pain, treatment with DSUVIA compared to standard care pain treatment in the ED improves Healthcare Professional Global Assessment (HPGA) of the Method of Pain Control and health care provider survey scores.

Scores to the HPGA will be based on a four-point scale. A 2x4 chi-square test will be used to compare the distribution of scores across the two treatment groups. An ordinal polytomous logistic regression model will be used to compare the distribution of proportions after controlling for stratification (sites) and baseline characteristics not balanced through random assignment. The same analysis will be repeated on the health care provider survey scores, with the modification to account for a five-level outcome.

Sample Size: The sample size calculations are based on the analyses of the primary aim (Aim 1) of the study. To detect a minimum effect size of 0.45, a sample size of 150 subject is needed (75 per group), assuming a type I error of 0.05, a two-sided alternative hypothesis, and 80% power. Thus, assuming a standard deviation of 21 (Karcioglu, 2003), a difference of 7.1 can be detected between the mean VNRS scores.

Missing data: Every attempt will be made to minimize the amount of missing data. Give the short time-window to collect data, missing data should be minimal. However, in the event that there is missing data for the outcomes, the pattern of missingness will be evaluated. Assuming that the data will be missing at random, multiple imputation techniques will be used to impute data and carry out the proposed analyses.

Subgroup: Analyses will be carried out for pre-defined subgroups, specifically: sex (male/female), Injury Severity Score (ISS $<$ or $\geq$ 16), age ($<$ or $\geq$ 50), blunt versus penetrating injury, history of prior opioid use (Y/N), air versus ground prehospital transport, transport origin (scene versus outside ED). For all subgroup analyses, regression models will be used to assess if there is a differential treatment effect by subgroup. Regression models will include main effects for treatment and the indicator of the subgroup, as well as the two-way interaction between treatment and the subgroup indicator. A statistically significant interaction will indicate a differential treatment effect.

Randomization of Ineligible Subjects: It is anticipated that there will be a small proportion of patients enrolled who receive DSUVIA or standard care that in retrospect will not have met the entry criteria and are thus ineligible. In this circumstance, patients will be analyzed according to the group to which they were randomized. Subgroup analyses based on eligibility criteria will be performed if the number of patients so affected is large. However, based on the relatively limited inclusion and exclusion criteria it is anticipated that the frequency of this event will be low.

Non-adherence: In some circumstances, patients may receive standard care instead of the DSUVIA intervention when randomized to DSUVIA. Non-adherence is most likely to occur in the case of the patient who requires intervention and despite DSUVIA being available, is unable to be provided. In the event of inappropriate handling or unsuccessful administration of the DSUVIA, a second dose of DSUVIA may not be administered. Once a physician has assessed the subject, if appropriate, the subject may receive a dose of standard care pain medication and continue in the DEEP study. Fortunately, this event is relatively rare. In keeping with the intention-to-treat analytic design, these patients will be analyzed with the group to which they were randomized.

Interim Analyses**:** Throughout the course of the study, the DSMB will review recruitment, retention, adherence to assigned intervention, data completeness, protocol deviations, and adverse events. Safety data will be examined on an ad hoc basis in the event that unexpected safety concerns arise from study data or from external research or literature.

The DSMB will review the primary and secondary outcomes bi-annually. Prior to initiation of the trial, the final monitoring plan will be developed to serve as the guide to the DSMB's decision-making process concerning early stopping of the trial. The interim analysis will consist of two components, efficacy evaluation and futility evaluation. The purpose of the efficacy evaluation is to detect early sign of treatment effect early in the study. The purpose of the futility analysis is to assess if the study is unlikely to achieve a statistically significant effect. In making the decision to recommend termination of the study, the DSMB shall be guided by several types of information: (i) a formal stopping rule based on the primary analysis (comparison of treatment groups on the primary outcome), (ii) information on safety outcomes by treatment group, (iii) consistency between results for primary and secondary outcomes, (iv) consistency of treatment effects across subgroups, and (v) conditional power.

We have designed this trial with one-interim analyses before the final analysis. The number of interim analyses will be finalized in discussion with the DSMB prior to the initiation of the study. The interim analysis plan is based on the Lan and Demets approach utilizing an O'Brien-Fleming spending function to

determine alpha spending and test boundaries. A formal interim analysis of efficacy will be performed when 50% of the randomly assigned participants have completed the assessment of the primary outcome. We will use a t-test to test for difference. The level of significance will maintain an overall p-value of 0.05 according to O'Brien-Fleming stopping boundaries leaving a p value of 0.003 and 0.049 for the interim and final analyses, respectively. This translates to a two-sided z-value for the interim and final analyses of +/-2.96 and +/-1.97, respectively.

In addition, the futility of the study will be evaluated at the time an interim efficacy test is conducted. Specifically, the conditional power will be calculated. If the condition power is less than value pre-specified by the DSMB (e.g., <20%), we can conclude that it would be futile to continue with the investigation.

Surveillance for Outcomes and Data Elements**:** Data will be collected prospectively as patient care progresses. This will include a review of the prehospital patient care report(s), ED and electronic/ paper hospital records.

In-Hospital Resuscitation Elements**:** Demographics, prehospital assessments and narcotic treatments, injury mechanism and characteristics, ED vitals, ED procedures/interventions, injury severity, injury severity scoring and assessment, ICU days and length of stay.

Data Entry**:** The DCC will create web-based HTML forms to collect necessary information from all participating sites. Web entry forms will have dynamic features such as edit and data type checks. Details and clarification about data items will be provided using pop-up windows. Data encryption and authentication methods will be used. Additional features will be built into the web entry forms including: forms transmission history, access to past forms, tracking of data corrections, and the capability to save and re-load incomplete forms. The subjects will be identified by a study number only. All clinical interventions will become part of the patient's medical records. All hard copy source documentation will be kept in a secured, locked cabinet in the site's research coordinator's office. All study documents will be maintained in a secure location for the time frame designated by each participating site's requirements. The electronic data will be entered and maintained on a password protected SSL website designed for this trial.

The data entered for the DEEP trial will be maintained by the DCC on a relational database. The database would be housed in a virtual environment so in the event of a hardware failure it would migrate to a new host. The data will be backed on a regular schedule with full transaction log files in use and copies of the data will be stored offsite with a secure service. In addition to the data server, the production web server will also be backed up routinely and as a virtual machine can be transitioned to different hardware automatically in case of hardware failure. All Servers are behind an enterprise firewall and access has to be granted through the firewall even within the University Network.

Database Management**:** A two-tiered database structure will be created. A front-end database will serve the web entry needs, using a database management system well-suited to handling updates from multiple interactive users. The data from this database will be transferred on a regular schedule to a data repository that can be used by statistical software packages. These datasets will be the basis for data queries, analyses and monitoring reports. Various versions of this database will be kept as needed, e.g. for quarterly performance reports. Access to data will be limited to those who need access to perform their tasks. The database management system is able to manage large quantities of data, to merge data from

multiple databases as required, to handle complex and possibly changing relationships, and to produce analysis datasets that can be imported into a variety of statistical analysis packages.

VII. Clinical Coordinating Center (CCC)

Clinical Coordination specific to the DEEP study will be performed by the LITES Network Coordinating Center and their dedicated research team at the University of Pittsburgh, including all regulatory requirements, provider and coordinator training and monitoring.

VIII. Data Coordinating Center (DCC)

Data Coordination specific to the DEEP study will be performed by the DCC and led by Dr. Wisniewski at the Graduate School of Public Health at the University of Pittsburgh. The DCC will coordinate all data collection and entry, management, security and confidentiality, data archiving, quality control and electronic medical record biomedical informatics as needed, as well as plan, coordinate and assist with all statistical analyses.

IX. Human Subjects

We anticipate that this study will be conducted utilizing a written informed consent while the patient resides in the ED.

Study Risks and Benefits:

Risks associated with pain management include allergic reaction, hypoxia requiring oxygen, (SPO2 < 90%), hypotension (SBP < 90 mmHg), or need for advanced airway management (placement of an endotracheal tube or supraglottic airway) following medication administration.

Regardless of treatment arm, we anticipate that enrolled subjects will benefit from increased monitoring of primary and secondary outcomes, specifically, a focus on adequate pain control and pain management complications including respiratory compromise, hypotension, decreased sensorium, and need for advanced airway control.

Institutional Review Board:

A central IRB at the University of Pittsburgh will be utilized for the regulatory needs of studies. All current LITES Network sites have IRBs which have experience and engagement with central IRB procedures.

Training and Participating Site Coordination:

As the clinical coordinating center for the trial, the University of Pittsburgh (LITES) at the University of Pittsburgh will be collaboratively responsible for all research coordinator training, provider training. Research coordinators, providers and associated staff will be trained during the months prior to the trial start date regarding the scientific basis for the study, specific inclusion and exclusion criteria, study procedures and SOPs. Training verification and retraining will occur if new staff is hired at individual participating sites.

X. Safety Monitoring

Adverse Event and Non-compliance definitions

a. *Adverse event* means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.
b. *Adverse reaction* means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

c. *Suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction"
d. *Reasonable possibility.* For the purpose of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
e. *Unexpected adverse event/reaction* refers to an event/reaction that is not consistent with the risk information described in the package insert and general investigational plan.
f. *Life-threatening, suspected adverse reaction.* A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.
g. *Serious, suspected adverse reaction*. A suspected adverse reaction is considered "serious" if, in the view of the Investigator (i.e., the study site principal investigator) or Sponsor, it results in any of the following outcomes: death, a life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
h. *Reportable non-compliance* refers to a failure on the part of the investigator or study team member to follow the terms of the IRB approved protocol or abide by applicable laws or regulations, that adversely affect the rights and welfare of subjects or significantly compromises the quality of the research data. Incidents of non-compliance on the part of the subject are not considered reportable.
i. *Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO)* refers to any accident, experience, or outcome that meets the following criteria: unexpected in terms of nature, severity or frequency; related, or possibly related, to a subject's participation in research; and places subjects or others at greater risk of harm (including physical, economic, or social) than was previously known or recognized.

Assessing and Reporting Adverse Events (AEs) and Non-compliance: Adverse events will be reviewed by the study sites and assessed for relationship to the study intervention. Investigators and study team will determine if any related adverse events occur during the period from enrollment through study participation termination. If reportable adverse events occur, they will be recorded on the adverse event case report form in the electronic data capture system, which will be submitted to the Coordinating Center. All reported adverse events will be classified by: a) Severity (fatal or life-threatening, serious, or non-serious); and b) Expected vs. Unexpected. An event will be determined to be unexpected if it is not consistent with the risks identified in the package insert or with the information provided in the general investigational plan. Please refer to the table below for timelines for reporting.

This study population is expected to have a relative low number of serious adverse events but will include death from trauma related injuries. Expected adverse events that are related or possibly related to the intervention will be documented and reviewed for changes in nature, severity, or frequency across the study population.

Organization	Unexpected, fatal or life-threatening suspected adverse reactions	Unexpected, serious, suspected adverse reactions	Expected adverse reactions	Reportable non-compliance	UPIRTSO
IRB	24 hours	10 working days	No reporting	10 working days	10 working days
Dept. of Defense	30 calendar days	30 calendar days	No reporting	30 calendar days**	30 calendar days*
DSMB	24 hours	7 calendar days	At next meeting (every 6 months)	At next meeting (every 6 months)	14 days*

*reported based on IRB determination that event is UPIRTSO
**reported based on IRB determination that non-compliance is serious or continuing

Data Safety Monitoring Board (DSMB)**:** A Data and Safety Monitoring Board (DSMB) will be created to review this study and provide recommendations regarding study continuation to the Sponsor. After initial approval and at periodic intervals (to be determined by the committee) during the course of the study, the DSMB responsibilities are to:

a. Review the research protocol, informed consent documents and plans for data and safety monitoring;

b. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, adverse events, unanticipated problems, performance of the trial sites, and other factors that can affect study outcome;

c. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;

d. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the study site Investigators;

e. Protect the safety of the study participants;

f. Report on the safety and progress of the study;

g. Make recommendations concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;

h. Monitor the confidentiality of the study data and the results of monitoring;

i. Assist by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

j. The DSMB will include experts in emergency medicine, surgery (trauma/critical medicine), bioethics and biostatistics. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.

k. The University of Pittsburgh Office of Clinical Research, Health Sciences will provide the logistical management and support of the DSMB. A safety officer (chairperson) will be identified at the first meeting. This person will be the contact person for serious adverse event reporting. Procedures for this will be discussed at the first meeting.

l. The first meeting will take place before initiation of the study to discuss the protocol, approve the commencement of the study, and to establish guidelines to monitor the study. The follow-up meeting frequency of the DSMB will be determined during the first meeting. An emergency meeting of the DSMB will be called at any time by the Chairperson should questions of patient safety arise.

XI. Quality Control, Assurance and Confidentiality

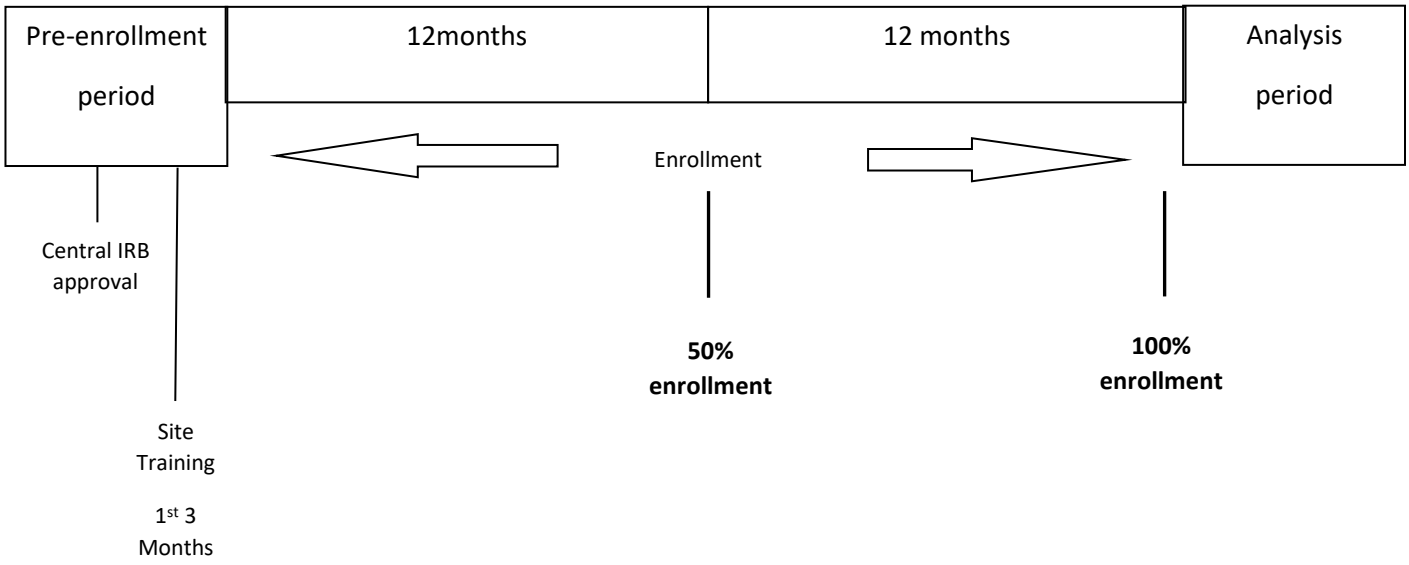
Protocol Compliance: The participating study site Investigators will not deviate from the protocol for any reason without prior written approval from the IRB except in the event of the safety of the research subject. In that event, the study site Investigator will notify the reviewing IRB immediately, if possible, and request approval of the protocol deviation, or, if prospective IRB approval is not possible, the study site Investigator will notify the reviewing IRB promptly following the respective protocol deviation. The study site Investigator will inform the reviewing IRB of all protocol deviations and unanticipated events involving risks to the research subjects and others, and will obtain prospective IRB approval for all proposed protocol changes. Persistent or serious noncompliance may result in termination of the study site's participation in the research study.

Protocol Deviations: Due to the relative focused inclusion criteria and the short intervention period, we expect few protocol deviations as compared to other large multicenter trials. If monitoring reports demonstrate evidence of continuing protocol deviations, we will analyze them to determine if they are site specific or common across the study. We will note if specific inclusion or exclusion criteria are being misinterpreted, if a certain time point in testing is being omitted, or if a common set of data elements are missing. If the deviations are site specific, retraining will be done at the site. If the problems are study wide, we will discuss them with the other investigators, the DoD and the IRB to see if the protocol needs to be amended or recruitment put on hold.

Privacy and Confidentiality: The study site Investigator's and members of their research team will make reasonable effort to ensure the research subjects' confidentiality. Subject name and other identifiable information will be kept in a secure, locked, limited access area.

Investigator Responsibilities: The study site Investigators will agree to implement the IRB approved protocol and conduct the study in accordance the ICH GCP Guidelines (E6, Section 5) as well as all applicable national, state and local laws. The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

Time Table:



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