1) Protocol Title

Effects of liposomal bupivacaine for acute pain in hip and femur fractures: a randomized, active comparator-controlled, blinded trial

DoD Additional Requirement:
This is an investigator initiated, single-center study funded by the United States Department of Defense Health Program. The UC Davis PI and research staff are aware of specific DoD requirements and confirm that all additional criteria for DoD research have been met.

2) Author of Protocol

- ☐ **UC Davis Researcher**
- ☐ **Researcher from other institution**
- ☐ **Private Sponsor**
- ☐ **Cooperative Group**
- ✓ **Other: Volunteer Associate Clinical Professor**

3) IRB Review History

This is our first revision to the initial submission to the IRB.

4) Objectives

This is an investigator-initiated, single-center, randomized, patient blinded, controlled trial. The purpose of this study is to compare the effect of a fascia iliaca compartment block (FICB) using 0.2% ropivacaine vs. liposomal bupivacaine in patients with femur and/or hip fractures admitted to the University of California Davis Medical Center (UCDMC). The primary endpoint will be the total opioid requirements during the 96 hour randomization period with secondary endpoints including total daily opioid requirements for days 1-4, duration of effect and objective pain scores using the numeric rating scale (NRS) during their hospital stay.

Hypothesis: In patients with femur or hip fractures, a fascia iliaca compartment block using liposomal bupivacaine will result in less total opioid administration during the randomization period compared to a fascia iliaca compartment block using 0.2% ropivacaine.

The long-term goal of this study is to provide pilot information to guide and design larger, multicenter trials which will evaluate the utility and cost-effectiveness of long acting liposomal bupivacaine as an opioid-sparring analgesic strategy in injured trauma patients. Ultimately, it is hoped that this information can improve safe and effective narcotic sparing analgesia in the awake, combat casualty, as well as serve as primary steps towards

evaluating broader considerations for liposomal analgesia to improve short- and long-term outcomes in these patients.

5) Background

Achieving adequate pain control in trauma patients proves challenging. Consequences of uncontrolled pain include immobility, respiratory compromise, exhaustion due to lack of sleep, disorientation, agitation, stress response, and post-traumatic stress disorder. The standard of care for analgesia in poly-trauma patients is the use of opioids administered via intravenous, epidural, or enteral routes with either intermittent dosing or as patient-controlled analgesia. Though opioid agents can provide effective analgesia, they exhibit untoward effects that at times may be dose limiting. These adverse effects include hypotension, bradycardia, central nervous system depression, respiratory depression, somnolence, and nausea. Additional common side effects of opioid use include pruritus, dry mouth, urinary retention, vomiting, prolonged recovery of ileus, and constipation. Clinicians are becoming increasingly aware of additional consequences, such as, opioid tolerance necessitating increased doses, opioid induced hyperalgesia, and opioid dependence. As such, increasing emphasis has been placed on a multimodal approach to the management of postoperative and post-traumatic pain. This multimodal approach includes use of local and regional blocks using local anesthetics.

The duration of standard local anesthetic formulations vary from 4-8 hours and administration can include single injections or continuous infusion catheters. Liposomal bupivacaine, Exparel®, has a prolonged duration of action of up to 96 hours. Studies have verified its safety with a very low risk of dysrhythmias, local tissue reaction, effects on wound healing or nerve toxicity. In the elective surgical setting, liposomal bupivacaine has been shown to have an opioid sparing effect, increased duration of analgesia, increased patient satisfaction, earlier discharge, and lower hospital cost. This formulation has not been studied in trauma patients and its novel use may impact practice in pain management of trauma patients. Patients may exhibit a lower opioid requirement with the use of the liposomal bupivacaine. In addition, this may reduce the incidence of untoward effects including respiratory depression, central nervous system depression, and gastrointestinal dysfunction, and subsequently speed recovery with improved mobilization and cooperation with physical therapy.
To date, no studies have evaluated liposomal bupivacaine regional analgesia following extremity trauma. This pilot study aims to assess the

efficacy of long-acting liposomal bupivacaine compared to ropivacaine 0.2% in orthopedic trauma patients with acute pain following femur or hip fracture.

6) Inclusion and Exclusion Criteria

Inclusion criteria:

1) age ≥18 years ≤ 70 years
2) Patient's s/p trauma, with confirmed femur and/or hip fractures with a planned admission to the hospital.
3) Patient is ambulatory without assistance (e.g. walker, cane, caretaker) prior to incident.

Exclusion Criteria:

1) >10 hours since presentation to the emergency department
2) History of seizure disorder, recent seizure or a document intra-cranial hemorrhage.
3) Central or peripheral neurologic deficit on presentation
4) Concern or compartment syndrome
5) Associated additional long bone fractures
6) End stage liver failure
7) Renal failure requiring dialysis
8) Pregnancy or breast feeding
9) Prisoners
10) Coagulopathy with INR >1.5
11) Use of direct thrombin inhibitors (bivalirudin, argatroban, desirudin, dabigatran etexilate), or direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)
12) Suspected prolonged intubation within first 12 hours secondary to respiratory failure other than peri-procedurally
13) Adults unable to consent
14) Pediatric patients <18 years old
15) Patients exhibiting signs of shock upon admission, HR >120 or SBP <100 mmHg.
16) History of allergic reaction to local anesthetics
17) Administration of any other local anesthetic in the 2 hours prior to the study enrollment.
18) Distal femur fractures

7) Number of Subjects

17 patients per arm
Total subjects: 34

8) Recruitment Methods

Subjects will be recruited from the UC Davis Trauma Center. Patients found to have femur and /or hip fractures admitted to UCDMC will be screened for eligibility.

Waiver of HIPAA authorization for recruitment is requested for access to PHI during the screening to determine eligibility.

Description of PHI that will be accessed.
Information reviewed to assess eligibility will include: date of admission, date of birth, gender, mechanism of trauma injury (blunt/penetrating), x-rays, lab results, admission vital signs, home medications and the patient's medical history.

The use of PHI involves no more than minimal risk and granting of waiver will not adversely affect privacy of the patients.
Access to medical records that contain patient's personal information for the purpose of this study will be limited to the approved research personnel. These personnel already have knowledge of and access to identifiable medical information of current trauma patients as part of their daily job functions; hence, granting of this waiver will not adversely affect the privacy of the involved patients or the confidentiality of their information. EMR access to PHI is password-protected and no PHI will be reused or disclosed to any

other person or entity, except as required by law. Data will be used solely for the purposes of determining study eligibility.

The research could not practicably be conducted without a waiver or alteration.
Without an initial review of the medical record for screening purposes, it would not be possible to identify potential subjects and confirm their applicability for study participation.

The research could not practicably be conducted without access to and use of PHI.
Since PHI is embedded in the medical record and since the screening process requires detailed information about trauma patients, access to medical records (viewing of PHI) is necessary.

9) Compensation to the Subjects

Subjects will not be compensated for this study.

10) Study Timelines

The duration of each subject's participation is the length of their hospital stay.

Duration anticipated to enroll all study subjects: 12 months.
Data acquisition and analysis: same 12 months
Manuscript preparation: 6 months
Total time requirement: 1.5 years

11) Study Endpoints

Hypothesis: In patients with femur or hip fractures, a fascia iliaca compartment block using liposomal bupivacaine will require less total opioid administration compared to a fascia iliaca block using 0.2% ropivacaine.

Primary Endpoint

(1) Total opioid requirement during the 96 hour randomization period measured in milligram morphine equivalents.

Secondary Endpoint

(1) Percentage of time during the 96 hour randomization period that the objective pain score was above mild (defined as a numeric rating score >4).

12) Procedures Involved

The nature of the risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent must be obtained before the subject can begin any screening procedures that are not considered standard patient care. Subjects who have undergone the screening procedures and have met the entry criteria will be randomized into the study and assigned to treatment by the Unblinded Pharmacist. Subjects will be randomized in a computer-generated, blinded block, 1:1 ratio to treatment with 60mL of either 0.2% ropivacaine (120mg) or a dilution of liposomal bupivacaine (266mg).

The Pharmacy and Emergency Medicine (EM) members will be the only unblinded study team members. All other members, including the Trauma team and Clinical Research Coordinator (CRC), will remain blinded.

The unblinded Investigational Drug Service (IDS) Pharmacy at UC Davis Health (UCDH) will be responsible for blinding and drug preparation. Investigational Product (IP) will be prepared in three 35mL Luer lok syringes, each containing 20mL of IP, for a total dose of 60mL. In addition to a patient-specific institutional label, masking/amber tape will also be affixed to the syringes in order to reduce the risk of drug recognition by a supporting procedure nurse. During the procedure, nursing care of the patient will temporarily transition from the primary bedside nurse to a supporting procedure nurse. The supporting procedure nurse will remain blinded and will assist primarily with assessments and recording of vital signs (but will not work directly with the IP).

For patients randomized to receive ropivacaine, IP will be prepared via straight draw of ropivacaine 0.2% (120mg) and equally divided into three syringes. For patients randomized to receive liposomal bupivacaine (266mg), a dilution will be prepared, using 20mL of liposomal bupivacaine (Exparel®) 1.3% (13.3mg/mL) and 40mL of 0.9% NaCl. While the stability of ropivacaine drawn into a syringe is longer than 4 hours at room temperature, in order to maintain the blind, all IP will be given a stability of 4 hours at room temperature.

The three syringes will be dispensed in a tamper-proof opaque bag and will be transported between the Pharmacy and Emergency Department by either a Pharmacy member or CRC. The tamper-proof opaque bag will contain a note of "CAUTION," that the content of the bag contain unblinding information.

The unblinded administering ED Physician will receive the IP and confirm that the opaque bag has not been tampered with. Prior to breaking the seal for drug administration, the unblinded ED Physician will ensure that the blinded primary nurse has transferred care to the unblinded procedure nurse, and that all blinded members of the healthcare team have left the exam room.

An unblinded Emergency Department staff will perform an ultrasound-guided fascia iliaca compartment block (FICB) per the institutional ER protocol, using 60mL of either ropivacaine 0.2% (266mg) or a diluted solution of liposomal bupivacaine (266mg).

The patient will be placed on a continuous pulse oximetry and telemetry monitoring. Using standard sterile technique, a dermal wheel will be created using 0.25% bupivacaine. Under ultrasound guidance, a blunt tipped needle will be inserted under the fascia iliacus muscle just inferior to the inguinal ligament and lateral to the neuro-vascular bundle. After a negative aspiration, the designated local anesthetic will be infused slowly over several minutes in 5 ml increments with aspiration between to the 5 ml increments to confirm extravascular insertion. The volume and dosing will be as listed above.
Immediately following the procedure, to prevent unblinding of blinded personnel, the syringes will be discarded per standard institutional procedures into opaque Sharps containers.Upon completion, the patient will remain on telemetry monitoring for 4 hours.

The patient will be blinded and all members of the healthcare team will be blinded from the point of transfer of care from the Emergency Department physicians to the receiving service.

Both groups will be able to receive as needed analgesia per the primary attending service. (e.g., oral hydrocodone/acetaminophen 5/325 mg or narcotic IV push as needed for breakthrough pain).

Patients enrolled in the study will be given a light blue wristband for identification to alert physicians regarding restrictions for anesthetics. Additionally, an automatic alert notification will be given by the Electronic

Medical Record system if additional local anesthetics are ordered for the patient.

Pain Assessment
Objective pain assessment will be evaluated by the UCDMC nursing staff per local standard of care which is every four hours while the patient is awake using a numeric rating scale (NRS) of 0 to 10 with a pain score of 0 being defined as: no pain, 1-4 mild pain, 5-7 defined as moderate pain, and 8-10 defined as severe pain.

Study Definitions
Acute and hospital-related adverse effects and study outcomes will be collected and tracked prospectively during the FICB and throughout the hospital stay, as appropriate per endpoint.

During hospital stay study outcomes
Data collection will include total amount of opioids administered to study patients in morphine equivalents (see Appendix) and the use of other analgesic medications during this time period. Adjunctive analgesic use including non-steroidal anti-inflammatory drugs, acetaminophen, and gabapentin will be quantified. Use of additional adjunctive agents such as muscle relaxants also will be collected.
All objective pain and agitation scores reported by the NRS will be collected; duration of supplemental oxygen requirement; number of episodes of oxygen desaturation (arterial O2 sat below 92%); morning incentive spirometer and peak flow measurements; 24-hour antiemetic (e.g., promethazine; ondansetron) pharmacotherapy; time to first bowel movement; and need for anti-hallucination or anti-delirium pharmacotherapy.
Additional outcomes: hospital lengths of stay; time from study drug initiation to maximum allowable ambulation per injury pattern; post-discharge opioid type and dosage provided at the time hospital discharge prescription; and patient report of chronic pain syndromes. Adverse effects including the incidence of hypertension requiring antihypertensive pharmacotherapy in addition to the patients home regimen, hypotension (SBP < 90 mmHg) requiring fluid bolus/vasoactive pharmacotherapy, tachycardia requiring pharmacologic intervention (defined as HR greater than 100 bpm), bradycardia (defined as HR below 60 beats per minute with symptoms or hypotension), respiratory depression (apnea; transition to higher level of respiratory support), emesis, hallucinatory reactions or experiences per patient interview, and pruritus per physical exam.

The study will be stopped if ≥2 patients receiving the active study drug develop the same Grade 3 adverse reaction (Adverse Event Severity

Definition defined previously) or if one patient develops a Grade 4 or higher adverse reaction.

13) Data and Specimen Banking

Not applicable.

14) Data Management and Confidentiality

Each patient will be assigned a unique study ID number at the time of study entry. Study information stored by the research personnel at UCDMC, which may include name and medical record number, will be kept strictly confidential and available only to the principal investigator and trained staff assigned to this study. All information will be kept secure in locked file cabinets accessible only by research personnel. All identifiers for recruitment purposes will be destroyed within 2 years of completion of study.

Statistical Analysis

Data will be presented as means ± standard errors of the mean (primary endpoint) and proportions ± interquartile ranges (secondary endpoint). Following assessment for normality, primary endpoint data will either be subjected to parametric unpaired two-sided t-tests or nonparametric Wilcoxon rank sum test Mann-Whitney two sample statistic. Significance will be set at $p = 0.05$. Secondary endpoint proportions will be assessed using either nonparametric chi-square tests or Fisher's exact test.

Other data such as ICU and hospital lengths of stay and adverse events will be collected, summarized, and described. Exploratory analyses these data may be attempted, but these will be hypothesis generating, given the small sample size used in this pilot study.

15) Provisions to Monitor the Data to Ensure the Safety of Subjects

This study involves minimal risk to the patient, however, the DoD requires an independent research monitor for all clinical studies and thus a medical monitor will be assigned. Dr. Gregory Jurkovich, MD, Professor of Surgery and Vice Chair of Surgery will act as the Data Safety Monitor for this study. Any unanticipated adverse event meeting grade 3 or grade 4 as listed below per the FDA's guidance for industry, will be reported to the study medical monitor. The medical monitor will keep a database if the reported events and will report any of the above adverse events to the FDA's MedWatch. In addition, subjects having experience an adverse

event of Grade 3 or 4 will be followed by the PI for the duration of their hospitalization.

The greatest risk for systemic toxicity is at the time of administration and most often as a result of inadvertent intravenous injection of the drug with rapid onset of symptoms. The procedure will be performed per UCDMC's "Hip Fracture Protocol" which includes routine fascia iliaca compartment blocks, a provider training protocol and routine ultrasound guidance. The protocol also includes telemetry monitoring, continuous pulse oximetry and q 15 min neurologic assessments for 30 min following injection. In addition, the patients will remain on telemetry for an additional 4 hours monitoring for any delayed events.

Following this 4 hour period, evaluation and capture of adverse events will continue until the completion of the 96 hour study period. This will consist of nursing evaluation and vitals every 4 hours around the clock and on an as needed basis. The study coordinator will evaluate for any potential events on a daily basis throughout the study period. The PI or co-PI will be notified directly of any severe adverse event at the time of the event.

The definitions of an adverse event are in line with the WHO-UMC system for standardized case causality assessment.

Causality term	**Assessment criteria***
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear

Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

The severity of the any potential reaction will be grade using the FDA's guidance for industry. They have been modified to meet the study characteristics and are listed below.

ADVERSE EVENT SEVERITY DEFINITIONS

Vital Signs *	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Dysrhythmia	Unsustained sinus or atrial rhythm < 10 seconds	Unsustained ventricular rhythm <10 secs in duration or sustained sinus rhythms that are asymptomatic	Any rhythm requiring treatment or a change in patient level of care	A ventricular rhythm >10 secs, requiring CPR, cardiac arrest, or any rhythm requiring continuous intravenous
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Dizziness	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV medication	Persistent or associated with a mechanical fall.
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Constipation	Dry, hard, painful stool.	No bowel movement for 48 hours	Requiring rectal suppository or enemas.	ER visit or hospitalization Requiring digital dissimpaction , colonic perforation.
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Methemoglobinemia	Less than 15%; mostly asymptomatic, cyanosis	15% or greater; cyanosis, lightheadedness, headache, tachycardia, fatigue, dyspnea, or lethargy	30% or greater; respiratory depression, altered sensorium, coma, shock, seizures	70% or greater; severe hypoxia, cardiac arrest

16) Withdrawal of Subjects

a) Stopping Criteria – This study involves a single dose medication; therefore, individual stopping criteria will not be related to the continued administration of study drug, but rather ability of the subject to continue to

participate in the follow-up evaluations. The following clinical situations and the methods of follow-up to deal with them are as follows:

(1) If a subject experiences an adverse event (AE) that renders them incapable of continuing with the remaining study assessments, the subject is to be discontinued. A final evaluation will be performed so that the subject's study participation can be terminated in a safe and orderly manner.
(2) Patients will be free to discontinue the study at any time, without prejudice to future treatment. These subjects will be encouraged to complete at least the remaining safety assessments.
(3) Patients will be removed from the study if they refuse either the study drug administration or fail to comply with study procedures.
(4) In the event that a subject chooses to withdraw from research after data collection has been performed, no additional data will be collected after time of withdrawal.
(5) There are no foreseeable circumstances necessitating the withdrawal of subjects from research without their consent.

b) Unblinding Criteria

(1) The blinding of therapy administered will be removed during the study period if evidence of local anesthetic toxicity is present based on the following:
   (a) Central nervous system reactions manifested by one of the following: paresthesia, acute anxiety, tinnitus or seizure.
   (b) Cardiac reactions manifested by one of the following: life threatening arrhythmia (ventricular arrhythmia, new onset heart block, new onset QT prolongation, hypotension unresponsive to fluid resuscitation or requiring vasopressor support or CPR.
   (c) Systemic Allergic reactions manifested by anaphylaxis.

17) Risks to Subjects

Pharmacologic risk:

Administrations of local anesthetics is common place in medical practice, however, there are adverse reactions. Those more frequent are listed below per each specific anesthetic.

Liposomal bupivacaine:

Very Common Adverse Reactions (≥10%): nausea, constipation, and vomiting.

Common Adverse Reactions (≥2% to <10%): pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, anemia postoperative, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain.

Ropivacaine:

Incidence of ≥5% in all clinical studies (N=3988): hypotension (37%), nausea (24.8%), vomiting (11.6%), bradycardia (9.3%), fever (9.2%), pain (8%), postoperative complications (7.1%), anemia (6.1%), paresthesia (5.6%), headache (5.1%), pruritus (5.1%), and back pain (5%).

Incidence 1 to 5%: Urinary retention, dizziness, rigors, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain, hypokalemia, dyspnea, cramps, and urinary tract infection.

There is also the potential risks of severe life-threatening adverse effects associated with the administration of local anesthetics which are due primarily to toxic systemic concentrations. Risks are associated with toxic plasma concentrations and can be characterized as central nervous system, cardiovascular and allergic reactions and local tissue toxicity. Despite the sustained release and potential for systemic toxicity, in studies to date, the safety profile of Exparel does not appear to differ in a clinically significant way from standard bupivacaine HCl. For the doses studied as part of the FDA clinical development program, there is no evidence that Exparel produces tissue toxicity in the short or long term, that it adversely affects wound healing, or that it is any more likely than bupivacaine HCl to cause neurological or cardiac toxicity with systemic absorption or inadvertent injection.

The greatest risk for systemic toxicity is at the time of administration and most often as a result of inadvertent intravenous injection of the drug with rapid onset of symptoms. As a result, FICBs will be administered in the emergency room where trained personnel and equipment are available to promptly treat patients who show evidence of neurological or cardiac toxicity. The procedure will be performed per UCDMC's "Hip Fracture Protocol" and will include telemetry monitoring, continuous pulse oximetry and q 15 min neurologic assessments for 30 min following injection. In addition, the patients will remain on telemetry for an additional 4 hours for monitor for any delayed events. The FICB is performed laterally, distant from the neurovascular bundle, and under ultrasound guidance minimizing the risk if intravenous injection. The lipid emulsion of the liposomal bupivacaine results in a white milky appearance similar to that of propofol. Steps taken to minimize inadvertent medication error include a recent manufacture change in propofol labeling and storage, handling and delivering of the study drug by the IDS at UCDMC. Patients that exhibit any of the signs or symptoms listed in 16b, will be removed from blinding and 20% lipid emulsion will be administered.

Privacy Risk

There may also be risks to the subject's privacy. The Researchers will store study records and other information about subjects in a secure location and will grant access only to those with a need to know.

Randomization Risk

Patients will be assigned to a treatment program by chance, and the treatment subjects will receive may prove to be less effective or to have more side effects than the other study treatments(s) or other available treatments.

18) Potential Benefits to Subjects

Subjects randomized to the liposomal bupivacaine arm may experience improvement in pain management, use of fewer opioids that may reduce incidence of untoward effects including respiratory depression, central nervous system depression, and gastrointestinal dysfunction and subsequently speed recovery with improved mobilization and cooperation with physical therapy.

There may be no immediate benefit to any patient involved in the study. However, future treatment may be influenced by the outcomes discovered in this study.

19) Vulnerable Populations

We do not intend to enroll subjects from vulnerable populations.

20) Multi-Site Research

Not applicable. This is a single institution based research study.

21) Community-Based Participatory Research

Not applicable.

22) Sharing of Results with Subjects

Any peer-reviewed manuscripts that result from this study will be made available to subjects upon request.

23) Setting

The study will be conducted at the UC Davis Medical Center located at 2315 Stockton Blvd., Sacramento, CA 95817.

24) Resources Available

All staff has also been delegated research specific responsibilities by the PI who is compliant and up to date with all required training:

1. Principal Investigator—Coordination of study activity, patient identification, collection of study data, reporting of results
2. Co-Principal Investigator—Collection of study data, patient identification, data entry, reporting of results
3. Co-investigator— Collection of study data and reporting of results
4. Co-investigator— Collection of study data and reporting of results
5. Co-investigator— Collection of study data and reporting of results
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16. Co-investigator— Collection of study data and reporting of results
17. Co-investigator— Collection of study data and reporting of results
18. Co-investigator— Collection of study data and reporting of results
19. ED Physicians- The unblinded ED physician will assist with collection of study data and reporting of results

20. Surgical fellow- Collection of study data and reporting of results
21. Pharmacist— drug acquisition, storage, randomization/blinding and administration.
22. Research Manager—Collection of study data, data entry, IRB management
23. Data Manager—data acquisition, data analysis, and electronic medical records review.
24. Research Coordinator— patient recruitment, administering consent, and performing data collection

25) Provisions to Protect the Privacy Interests of Subjects

In the emergency department, potential subjects will be approached by one of the PI's or clinical research coordinator to gauge interest in participating. If the subject declines, no other attempts will be made.

In order to help the subjects feel at ease, all conversations will be discreet and will occur in private patient areas.

Only the PI and research staff is permitted to access information about the subject in regards to the study.

26) Compensation for Research-Related Injury

Subjects are instructed that it is important they promptly tell the person in charge if they believe that they have been injured because of taking part in this study. For subjects who are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or may be billed to the subject's insurance company just like other medical costs.

27) Economic Burden to Subjects

There are no perceived costs for subject participation in this study.

28) Consent Process

- Consent will be performed by either one of the PI's, co-investigators or a clinical research coordinator.
- Consent will take place at UC Davis Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817.

- Prospective subjects will be provided the consent form in person during their hospital admission. They will be given sufficient time to review the consent form and discuss with friends and family. We will ensure that subjects' questions have been answered prior to the consent form being signed.
- Patients will be re-consented if changes to the protocol affect their study involvement or the risks change.
- The PI will be following "SOP: Informed Consent Process for Research (HRP-090)."
- Potential subjects will be advised that study participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which they would be otherwise entitled. They will be advised that participation in this study may not provide any benefit(s) to them. They will also be advised of the potential risks and alternate treatment options, and they will be given sufficient time to consider their decision.
- Subjects must be at least 18 years old to participate in this study.

HIPAA Authorization for Research

A HIPAA Authorization will be signed by each subject during the initial consent process.

Non-English Speaking Subjects

Non-English speaking subjects are not excluded from participation in this study. For potential subjects who do not speak English, current UC Davis IRB policies HRP-090 and HRP-091 for enrolling such subjects will be adhered to.

Waiver or Alteration of the Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)
N/A

Subjects who are not yet adults (infants, children, teenagers)
N/A

Cognitively Impaired Adults

This study is not designed to enroll cognitively-impaired subjects.

29) Process to Document Consent in Writing

Informed consent for this study will be documented in writing per SOP HRP-091, Written Documentation of Consent.

30) Drugs or Devices

The blinding and drug preparation will be performed by the investigational

drug service (IDS) at UCDMC. Following informed consent, patients will undergo computer generated, blinded block, 1:1 randomization. The blinding will be maintained up to the time of breaking the seal for drug administration. Necessary measure will be followed to maintain patient blinding. An ultrasound guided fascia iliaca compartment block (FICB) with either 266mg (60 ml) of liposomal bupivacaine or 120mg (60 ml) of 0.2% ropivacaine. Both groups will be able to receive as needed analgesia per the primary attending service. (e.g., oral hydrocodone/acetaminophen 5/325 mg or narcotic IV push as needed for breakthrough pain). Patients will remain blinded throughout the hospitalization.

a) The involved drugs are:
   i) Liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals, Parsippany, NJ) is a long-acting formulation of bupivacaine HCl, an amide-type local anesthetic/analgesic that is FDA approved for single dose infiltration into a surgical site to provide post-surgical analgesia. After local administration, bupivacaine is slowly released from the liposomes resulting in prolonged plasma levels and analgesia for 96 hours.
   ii) Ropivacaine HCl(Naropin®, AstraZeneca Pharmaceuticals) is an amide-type local anesthetic/analgesic which is FDA approved for local and regional anesthesia for acute pain management. This includes local infiltration, regional nerve and epidural blocks, both single dose and continuous infusion.