LIBERATE-LIposomal **B**upivacaine v**ER**sus **A**djuncts in **T**otal should**E**rs

Background:

Pain control after orthopedic surgery can be challenging, especially in light of the goals of shortened hospital lengths-of-stay, reduced opioid consumption, and increased patient satisfaction. With the estimated incidence of new persistent opioid use of 6.5% after surgery in the U.S. [1], reducing opioid consumption (and therefore the potential for addiction) has become a major objective in today's healthcare environment. A multimodal analgesic approach that includes non-opioid medications and peripheral nerve blockade with local anesthetic is rapidly gaining popularity as a means to accomplish this goal. Previous studies have demonstrated that the addition of adjuncts, such as dexamethasone, to local anesthetics can prolong peripheral nerve blockade to greater than 24 hours postoperatively [2–4], [5] . It has also been shown that adding non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and gabapentin to pain control regimens in addition to peripheral nerve blockade decreases opioid consumption and hospital length of stay.[6]

In 2011, the FDA (Food and Drug Administration) approved liposomal bupivacaine (Exparel®), a sustained release formulation of bupivacaine, for surgical site infiltration. Liposomal bupivacaine has been described as providing prolonged analgesia for up to 72 hours when administered as an infiltrative technique. [7] There have been few studies investigating liposomal bupivacaine and its effect on pain relief and opioid consumption. The majority of these studies focus on an intraoperative infiltrative technique by the surgeon as compared to single injection peripheral nerve blockade with mixed results that trend towards a lack of a statistical difference between the two [8];[9];[10]. There are limited studies demonstrating its superiority over standard local anesthetics, like bupivacaine, in perineural blocks. [8,9,11–13] Only one study thus far has examined the use of liposomal bupivacaine for interscalene peripheral nerve blockade, [12] but it was not until April 2018 that liposomal bupivacaine was FDA-approved for use in interscalene peripheral nerve blockade. Given the limited amount of evidence comparing liposomal bupivacaine to bupivacaine with additives in peripheral nerve blockade, it is unclear whether liposomal bupivacaine can provide longer analgesia (as evidenced by time to first opioid) or can reduce opioid consumption as compared to standard local anesthetic with additives.
In this study, we are seeking to compare our standard approach of a single injection interscalene brachial plexus blockade using bupivacaine 20 mL 0.5%, 5 mg dexamethasone, and 5 mcg epinephrine to the same volume of a single injection interscalene brachial plexus blockade using liposomal bupivacaine mixed with bupivacaine 0.5%. The primary endpoint of the study is the total amount of opioid consumed in morphine milligram equivalents (MMEs) by the patient postoperative days 0 through 3 (PODs #0-3) for primary total shoulder arthroplasty (TSA) patients, including anatomic and reverse TSA.

Purpose/Aim:

We are seeking to evaluate the effect of liposomal bupivacaine (10ml liposomal bupivacaine 133 mg mixed with 10 mL of 0.5% bupivacaine for a total volume of 20 ml of injectate) in a single injection interscalene brachial plexus blockade, as compared to our standard approach single injection interscalene brachial plexus blockade using bupivacaine 0.5% + 5 mg dexamethasone + 5 mcg epinephrine (20 mL volume ofinjectate).

Our primary endpoint is the total opioid consumption postoperative days 0 through 3 (PODs #0-3) after TSA, standardized to morphine milligram equivalents (MMEs).
Secondary endpoints include:

- Time to first opioid medication
- Pain assessment at post anesthesia care unit (PACU) arrival, PACU discharge, POD #1, POD #2, POD #4, and POD #60 using questions from the Modified Brief Pain Inventory (MBPI)
- Hospitallength-of-stay
- Assessment of patient overall satisfaction with pain control on a scale from 0 = very dissatisfied to 10 = verysatisfied.
- Incidence of distress from block numbness on a scale of 0 to 10 with 0 = not at all and 10 = very much (adapted from the Overall Benefit of Analgesia Score)
- Duration of sensory and motor nerve block while in the hospital
- Notation of adverse postoperative events or block complications up to 60 days after surgery including:
    - Postoperative nausea/vomiting (PONV), as defined by non-prophylactic administration of antiemetics during hospital stay within 24 hours post-operation
    - Local anesthetic systemic toxicity (LAST) as defined by any treatment for this condition during hospital admission
    - Postoperative neurologic symptoms (PONS) as defined as sensory or motor dysfunction in appropriate anatomic distribution of block present at >4 days post-surgery [14]
    - Postoperative ED visit or readmission due to uncontrolled pain within 60 postoperative days
    - Bleeding/hematoma at the site of local anesthetic injection that develops prior to discharge from the hospital
    - Hospital readmission within 30 days from discharge

Hypothesis:

We hypothesize that using liposomal bupivacaine in interscalene brachial plexus blockade will result in a reduced total opioid consumption (in MMEs) during postoperative days 0 through 3, as well as increased duration of blockade (represented by time to first analgesic dose).

Study Design:

This will be a single-center, prospective, randomized controlled cross-sectional study comparing the total opioid consumption during postoperative days 0 through 3 in two groups of patients undergoing primary TSA, both anatomic and reverse. The individuals collecting data will be blinded to the patient's randomization group. Due to the differences in appearance of the medications used, blinding of the individual performing the procedure will not be possible as the anesthesiologist will see the medication when assessing for intravascular needle placement. IRB approval was obtained.

Human Subjects:

Inclusion Criteria:

Patients meeting *all* of the following criteria will be included:

- Patient age ≥18 years, with no upperlimit
- Lack of languagebarrier
- Informed consentobtained
- Presenting for primary total shoulder arthroplasty (TSA), both anatomic and reverse, by a specialty-trainedsurgeon
- American Society of Anesthesiology (ASA) physical status score I- III

Exclusion Criteria:

Patients meeting *any* of the following criteria will be excluded:

- Presence of a language barrier
- Inability to complete telephone and/or paper questionnaire
- Lack of consent
- Allergy to local anesthetic
- Inability of patient to participate in standard multimodal pain regimen (i.e. tylenol, celecoxib, ibruprofen, or opiods)
- Chronic pain syndrome and/or preoperative opioid use > 50 MME per day (including extended-release formulations and methadone)[15]
- Preoperative consultation to chronic pain service
- Active medical or recreational use of inhaled/ingested marijuana/cannabinoid products
- History of (<3 months) or current substance abuse, including any illicit drugs or excessive alcohol consumption as defined by the Office of Disease Prevention and Health Promotion (4 or more drinks per day or 8 or more drinks per week for women and 5 or more drinks per day or 15 or more drinks per week formen)[16]
- Baseline peripheral neuropathy of the brachial plexus
- Contraindication to receiving single shot peripheral nerve blockade; including antithrombotic medications as per most recent American Society of Regional Anesthesiology (ASRA) guidelines [17] , coagulopathy or coagulation disorder, or infection at injection site
- Severe chronic obstructive pulmonary disease (COPD) or other significant pulmonary disease where interscalene nerve block would be contraindicated due to concern for respiratory failure from phrenic nerve palsy
- Weight < 45 kg, given concern for local anesthetic toxicity at dosages given for the study
- ASA score IV-V
- Revisionarthroplasty
- Anatomic abnormality that limits or prevents the patient from receiving an interscalene nerve block
- Pregnant, nursing, or planning to become pregnant during the study or within 1 month after the shoulder replacement surgery

Post-Enrollment Exclusion:

- Block failure, as defined by a lack of sensory and motor blockade over incisional areas/shoulder
- Loss to follow-up after hospital discharge

Procedures/Methods:

The surgeon's medical executive assistant will notify the research team when a total shoulder arthroplasty surgery is booked with the surgeon. During the surgeons' preoperative visit with the potential subject, the surgeon will explain the patient potentially will be approached during their PREPARE visit for this study. The research team will screen the potential research subject, and patients will be approached and consented for the study in the preoperative PREPARE clinic by a member of the research team, with an attending anesthesiologist or regional anesthesia fellow on the acute pain service immediately available to answer any questions regarding the study (see consent form).

Details of the procedure are as follows: Prior to any procedure, the patients are checked into the preoperative holding area (POHA), surgical consent is reviewed, and the patient's operative site is marked. A preoperative assessment of the patient's motor and sensory function of the operative extremity will be performed to establish a baseline to compare to postoperative function. Motor function will be assessed by shoulder abduction and elbow flexion using the Oxford scale of muscle strength grading [18]. Sensory function will be assessed on the shoulder by assessing sensation to a pin prick on the shoulder in the axillary nerve distribution using the end of a paperclip. The sensory function will be measured using a 4-point scale (0-3) with 0 = no sensation, 1 = sensation to pressure only, 2 = paresthesia, and 3 = full sensation. A peripheral intravenous catheter is inserted and standard monitors, including pulse oximetry, blood pressure monitoring every 5 minutes, and 3-lead EKG are applied. Nasal cannula oxygen at 2L/min is administered. All patients receive mild sedation with midazolam or propofol prior to peripheral nerve blockade. Patients are positioned in a 45-degree semi-upright position with the head turned to the contralateral side of surgical site.

Single injection interscalene brachial plexus blockade is performed by one of 3 regional anesthesiologists or by one of 3 regional anesthesia fellows under the direct supervision of 6 attending regional anesthesiologists. A high-frequency linear ultrasound transducer is used to locate the brachial plexus at the level of the nerve roots in the neck (interscalene approach). Ultrasound guidance is utilized to monitor the distribution of local anesthetic deposited via a 22G short bevel needle using an in-plane approach. In the control group, the local anesthetic solution consists of bupivacaine 0.5% + 5 mg preservative-free dexamethasone + 5 mcg epinephrine for a total of 20 mL volume deposited perineurally. The liposomal bupivacaine group consists of a total of 133 mg (10 mL) liposomal bupivacaine + 10 mL 0.5% bupivacaine (to account for early block coverage) for a total of 20 mL volume deposited perineurally. Injection of local anesthetic will be achieved with a 10mL syringe under low pressure and with frequent aspiration performed to minimize risk of intravascular injection. During the nerve blockade, patients will be mildly sedated with intravenous midazolam or propofol with the goal to remain conversive, especially with regard to the occurrence of any paresthesias during block placement for safety purposes. Due to the difference in physical appearance of the study and control medications, the syringe of medication for injection will be held under an opaque towel during the block procedure so the patient remains blinded.

After placement of the single injection brachial plexus block and prior to induction of general anesthesia in the operating room, the patients will be evaluated for block failure with an assessment of motor and sensory function in the same manner performed pre-nerve block. The time of this assessment will be recorded to monitor the time from block placement to the time of assessment. At least 15 minutes should elapse between block placement and the pre-induction assessment of motor and sensory function.

The patients will be taken to the operating room (OR) for their primary TSA procedures, as performed by a specialty-trained shoulder surgeon. A standardized multimodal analgesic regimen for all patients will be followed, including preoperative oral acetaminophen 975 mg and celecoxib 200 mg if there are no contraindications to these medications. Medications administered preoperatively will be evaluated via query of electronic medical record (EMR). Intraoperatively, induction of general anesthesia will be achieved using propofol 1-2 mg/kg, fentanyl 1-3mcg/kg, and lidocaine 0.5-1 mg/kg followed by paralyzation with rocuronium 0.5-1 mg/kg prior to securing the trachea with endotracheal tube. IV fentanyl will be given periodically during the intraoperative course as needed for pain control. IV decadron will not be given for prophylaxis of postoperative nausea and vomiting, alternative medication will be utilized as deemed appropriate by the attending anesthesiologist. Medications administered intraoperatively will be evaluated via query of electronic medical record (EMR). Postoperative analgesia in the post-anesthesia care unit (PACU) will consist of intravenous hydromorphone and/or fentanyl as needed. Medications administered in the PACU will be evaluated via query of electronic medical record (EMR).Postoperative analgesia after PACU discharge and while on the floor will consist of of scheduled acetaminophen, scheduled NSAID (celecoxib or ibuprofen), and as-needed opioid medication (oxycodone, hydromorphone, or tramadol depending on patient requirements and tolerances).

All patients will be receive an in-person evaluation at the time of post-anesthesia care unit (PACU) discharge and on the morning of POD #1 using questionnaires modified from the validated Modified Brief Pain Inventory [19] (see attached questionnaires). Patients will receive a sensory and motor exam on the operative side in the PACU and on POD#1 prior to discharge. Medications administered during admission will be evaluated via query of the electronic medical record (EMR) system. Most patients are discharged home in the afternoon of POD #1. They will be discharged home on the standard of care pain regimen, which is similar to their in-hospital pain regimen as prescribed by the surgical team.

On POD #2, POD #4 and POD #60, if the patients have been discharged, they will be called via telephone and asked questions from a questionnaire regarding overall pain control and the amount of pain medications consumed each day. (See the following Questionnaires). Prior to discharge, the patients will be given and educated on using a medication diary (see medication diary), by a member of the research team, which they will mail back using an addressed, stamped envelope. On the medication diary, patients will record the number of opioid pain pills they took POD#1-3. The medication diary will also be used for the patients to record their maximum, minimum, and average pain scores for each day using a 0 to 10 scale. Patients will be asked to read back the information from this diary during phone calls on POD #2 and POD #4. Patients will be asked the time that they first noticed their block wearing off. During the POD #4 phone call, patients are reminded to return their medication diary by mail in the provided envelope. In the event that a patient's medication diary is not received, a research team member will attempt to contact the patient up to two times to remind the patient to return the medication diary via mail. Patients will be provided with a 24/7 pager number to reach the on-call physician for the acute pain service for any questions that might arise after discharge with regard to their peripheral nerve blockade.

To assess for PONS, at the time of postoperative follow-up with the patient's orthopedic surgeon, the patient will be asked by the orthopedic team if they have any persistent numbness, tingling, or paresthesias of their operative extremity. The patients will also be asked about any of these symptoms during the phone calls in the first 3 postoperative days, as well as on the POD #60 questionnaire. If the patient reports these symptoms, the patients will be asked to describe the location, severity, and type of sensory changes they are experiencing as well as any aggravating or alleviating factors.

Baseline demographic data and comorbidities for participants in each group will be collected using the EMR system, including: gender, age, body mass index (BMI), ASA class, home medications, and history of hypertension (HTN), chronic obstructive pulmonary disease (COPD), hyperlipidemia, diabetes, rheumatoid arthritis, and chronic steroid use. Additionally, the EMR will be used to collect information on duration of surgery (min), duration of time to perform the block (min), length of PACU stay (min), time to discharge home (hrs), time to first dose of opioid medication (hrs), incidence of postoperative nausea and vomiting (as defined as receiving one or more antiemetic medications postoperatively in non-prophylactic administration) and incidence of complications from peripheral nerve blockade.

Randomization/Blinding:

Randomization will be performed using https://www.randomizer.org in 1:1 fashion. Due to the difference in physical appearance of the control and study medications, the anesthesiologist(s) performing the nerve block will not be blinded. The individuals collecting study data as well as the patient will be blinded to the randomizationassignment.

Risks/Benefits to the Patient:

Patients will be randomized to receiving a single interscalene injection using either (1) bupivacaine 0.5% + adjuncts or (2) liposomal bupivacaine + bupivacaine 0.5%. Interscalene single shot peripheral nerve blockade is currently part of the standard of care for pain control in the total shoulder arthroplasty population at our institution.

Potential Risks:

Potential risks to the patients can be found on the provided consent form. Risks associated with peripheral nerve blockade are variable and often secondary to equipment, techniques, and anatomic location. General risks of peripheral nerve blockade include risk of block failure, bleeding/hematoma formation at the site of needle entry, infection, potential allergic reaction to local anesthetic solution, including its liposomal, dexamethasone, or stabilization additives, intravascular injection leading to local anesthetic systemic toxicity (LAST), and transient or permanent neuropathy.[20–23] With regards to the interscalene location of the injection, additional risks include the potential for hoarseness,[24] dyspnea, [2526] respiratory distress and phrenic nerve palsy resulting in hemidiaphragmatic paralysis, [22 10,22,27,28] as well as rare case reports of inadvertent injection into the epidural or intrathecal spaces[29];[30]. Additionally, there has also been documented hemodynamic instability in patients receiving interscalene blocks who are then in the sitting position during surgery[31, 32, 33]. Patients will be informed of these risks during the consent process.

Potential Benefits:

Peripheral nerve blockade has been found to improve postoperative analgesia and decrease opioid requirements. Previous studies also suggested that patients who receive a single injection brachial plexus blockade for TSA have increased patient satisfaction and increased range of motion. [34] Interscalene blockade is the current standard of care for shoulder arthroplasty at our institution. Patients receiving liposomal bupivacaine may have a prolonged analgesic effect and take fewer opioid medications than those who receive our standard practice of bupivacaine with additives. Patients will be informed of these benefits during the consent process.

Adverse Events:

Adverse events that occur during the regional anesthetic procedure will be noted immediately by the regional anesthesia team/provider with immediate management. Adverse events which occur during the patient's hospitalization will be reported to the acute pain/regional anesthesia team via a 24/7 paging system, which will result in prompt in-person evaluation and management. Adverse events include, but are not limited to, bleeding/hematoma at site of needle entry, allergic reaction to local anesthetic medication, infection at site of needle entry, transient (or rarely permanent) neurological dysfunction including dysesthesia or paresthesia, hemodynamic instability both intraoperatively and postoperatively, hoarseness, phrenic nerve palsy, dyspnea, or respiratory distress, or potential inadvertent injection into epidural or intrathecal space.

Adverse events or patient concerns that occur up to 60 days post-discharge will be communicated to the on-call physician via the 24/7 pager for the acute pain service. This will prompt a return phone call to the patient to discuss the concern. If there is a need for urgent in-person patient evaluation, the patient will be instructed to come to the emergency department where they will be evaluated by that on-call physician upon arrival.

Data Safety and Monitoring Plan:

Risk assessment:

Greater than minimal risk

Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

The risks associated with the current study are deemed greater than minimal for the following reasons:

1. We do not view the risks associated with the interscalene brachial plexus nerve block procedure as minimal risk.
2. We do not view the risks of sedation for peripheral nerve block procedure as minimal risk.
3. We do not view the risks associated with peripheral nerve block procedure as minimal risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator according to the following categories:

a. Definite: Adverse event is clearly related to investigational procedures(s)/agent(s)
b. Probable: Adverse event is likely related to investigational procedures(s)/agent(s)
c. Possible: Adverse event may be related to investigational procedures(s)/agent(s)
d. Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s)
e. Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s)

Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverseevent
3. Severe adverse event

Plan for Determining Seriousness of Adverse Events:

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the followingoutcomes:

1. Death
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization
3. A persistent or significant disability or incapacity
4. A congenital anomaly or birth defect
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is

important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Plan for reporting unanticipated problems involving risks to subjects or others (including adverse events) to the IRB:

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the HHC IRB in accordance with HHC IRB Policy, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policywill be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.**

Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies:

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

1. All Co-Investigators listed on the protocol

The principal investigator will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Data Use, Collection, Storage and Security:

Data collection and follow-up will be performed by research team physicians, research coordinators, assistants, and nurses. The physician(s) will only collect data for patients in which they did not participate in the nerve block placement in order to avoid bias. Data collection with regard to baseline demographics and surgical information, including type of surgery (anatomic vs reverse) and surgeon will occur via query of the EMR system. Patient pain scores and the amount of opioid administered (in

MMEs) will be obtained via in-person interview and query of the EMR system (during POD #0-1), via telephone call/questionnaire (POD #2, POD #4), and through the patient's mailed-in pain diary. If we are unable to reach the patient on the first phone call attempt, two additional attempts will be allowed in any given day. If the patient is not able to be reached on POD #4, up to 3 attempts will be made on POD #5 in order to complete the POD #4 questionnaire. Should the opioid diary not be received in the mail, but the patient was able to read all of the data over the phone to us on POD #4 or #5, we will use the data they provided over the phone. Should the patient provide all of the data over the phone on POD #4 and then mail in the diary, we will default to the medication diary. If patients are unable to be reached via telephone during the data collection period (POD #1-5) but return by mail a completed opioid diary, the data from the diary will be included in the data analysis. Should patients be lost to follow-up prior to collecting all of our data, these patients will not be included in the data analysis for our primary endpoint.

Data in one hard-copy format will be stored in a binder associated with each patient which will be kept in a double locked office with restricted access to only the individuals involved with data collection and analysis. After study conclusion, the binders will be kept in locked office for a period of 6 years. Data with all identifying patient information removed will be stored in the secure database REDcap. Access will be restricted to members of the research team involved in performing blocks, collecting data, and/or analyzing data and granted on a case-by-case basis by the PI. Additionally, IRB approval will be obtained and all key personnel (all individuals responsible for the design and conduct of this study) have completed CITI Human Subjects Protection Training.

MMEs for the opioids given during the study period will be calculated using an equivalency chart obtained from www.cms.gov (see citation below). The formula to calculate MME is as follows: Strength per Unit X (Number of Units/ Day) X MME conversion factor = MME/Day. The calculation will be repeated for each postoperative day during which data is collected.

Data and Statistical Analysis:

Demographic data amongst both groups will be analyzed after collection. Preliminary analysis will be done to determine the distribution of all continuous variables and the appropriateness of parametric data analyses. Descriptive data will be produced, mean and standard deviation for continuous variables where the assumption of normality ismet, median and interquartile range for continuous variables that are not normally distributed as well as ordinal data. Frequencies and proportions will be described for all categorical data. The primary analyses will compare the MME of opioids taken postoperatives days (PODs #0-3) and the total for the four days. If distributions have been shown to be normal, an independent groups t-test will be run; alternatively a Wilcoxon Ranked Sum test will be done if there are distribution issues. Similar analyses will be done for reported pain and nausea scores. The time until first post-op analgesia, PACU and hospital lengths of stay and the other timing measures are likely to be skewed and thus the Wilcoxon Ranked sum test will be used for the analysis. Complication data will be analyzed using chi square tests of proportion. To the extent that the sample size allows, subgroup analyses will be done by surgeon, by type of surgery (anatomic vs reverse) and by demographic characteristics of the patients to explore if any of these interact with the effects of the block medications.

Power Analysis and Sample Size:

A power calculation was done based on the primary outcome of postoperative days 0-3 use of opioid medication. As Exparel was only FDA-approved for use in interscalene peripheral nerve blockade in April 2018, we were not able to find empirical data for the comparison proposed in this study. Hannah et al compared intraoperative liposomal bupivacaine with single injection interscalene nerve block of ropivacaine. While not the same comparison, we felt this would offer good guidance for effect size and our power calculation. Hannah et al reported large differences for the use of opioid medication in the two groups for postoperative days two and three (comparisons of 112 mg to 37 mg morphine equivalents for day 2 and 20 mg versus 5 mg morphine equivalents for day 3). As they unfortunately do not report the related standard deviations, the effect sizes were 'back calculated' based on their sample size (groups of 37 and 21) and reported p values ($p = .001$ and $p = .002$). This resulted in estimated effect sizes of .84 and .74 for the two days. To achieve 80% power with an overall significance rate of .05, for an independent group t –test, sample sizes of 24 and 30 per group would be needed to detect these large effect sizes. Although the follow-up period is quite short for the primary endpoint of opiate consumption in postoperative days 0 through 3and prior experience has shown excellent record of communicating with these patients by telephone for the three day period (length of stay is usually one postoperative day), we still feel it is imperative to increase the proposed sample size to account for attrition. Assuming a loss-to-follow up rate of 25%, we propose a sample size of 40 patients per arm of the study with the total number of 80 participants.

An interim analysis will be done when approximately half (40) of the patients have completed surgery and at least POD4 medication data. The timing coincides with the departure of the one surgeon involved from HHC. If the continuation is approved and the interim analysis data indicate reason to continue the study, one or more different surgeons will be recruited to participate and the sample size adjusted . The interim analysis will provide basis for the power calculation to be redone with better empirical evidence on this situation rather than extrapolation from similar data. Finally, this timing also coincides with the first IRB renewal for the project. A full reporting of all adverse events is included in the continuation and will serve as the information for a safety review. These will be reviewed by the IRB prior to the interim analysis (plan is for simultaneous review of the continuation and this modification).

The interim analysis will focus on the total post operative MMEs reported for days 1-4 for each day, (days 0-4) and for the total use of opioids during this period. The time until the first administration of post-op analgesia will also be part of this analysis. As described above, each of the analyses will be done using either t-tests for independent groups or Wilcoxon Ranked Sum tests; we are anticipating skewed distributions for MME and time and thus expect the Wilcoxon statistic to be used. As is standard, a p value of .05 will be used to indicate statistical significance for all tests. In order to maintain this type one error rate over the entire study, the O'Brien- Fleming method for alpha spending will be used to determine the significance levels that will be used for the interim ($\alpha = .0054$) and final ($\alpha = .0492$) analyses.

If the continuation of the study is not approved by the IRB, the interim analysis will not be completed as the study will beclosed.

If the reported MMEs for the patients who received the liposomal bupivacaine are significantly lower ($p < .0054$) than for patients receiving the standard of care, the study will be stopped as having demonstrated a significantdifference.

If the difference in opioid use between the groups is smaller than what the principal investigator and co-investigators determine to be clinically meaningful and/or the redone power calculation indicates the need for a sample size that is so large as to not be feasible, the study will be stopped as futile.

The completion of the interim analysis in April, 2020 (detailed report appended) using a total of 40 patients resulted in findings that showed a difference between the group with the potential for clinical relevance but that did not reach the level of statistical significance. The decision was therefore to continue the study. A revised sample size calculation was conducted based on the analysis of post-operative use of opioids (total for days 1-4) as evidenced in the interim analysis data set. With a distribution that did not meet assumptions of normality for use of parametric analysis and included several outlier values, the calculation was done using group medians in place of group means and an estimate of pooled standard deviation derived from the interquartile range.[35] Using these parameters, a power calculation suggested 39 patients in each group. This was raised to reflect the relative power of independent groups t-test and Wilcoxon Ranked Sum test (the latter equal to .955 of the power of the former) and a 10% attrition rate, consistent with the interim data availability for days 1-4.[36] The final calculation with these adjustments indicates the need for 45 patients in each group to achieve 80% power to detect differences equal to or greater than that found in the interim analyses with a significance level of .05. Due to the rate of attrition seen in the study during the accrual of the 45 subjects per group, the sample size is increased to 55 subjects per group to achieve 90 subjects with full data sets.

Clinical Significance:

We seek to examine whether liposomal bupivacaine injected into the interscalene brachial plexus location reduces the total amount of opioid consumed postoperatively, reduces pain scores, or lengthens duration of analgesia as compared to the standard use of bupivacaine with adjuncts. Should we find that liposomal bupivacaine is able to reduce the amount of opioids consumed postoperatively, it may contribute to a decreased risk of chronic opioid addiction. Should liposomal bupivacaine be found to not reduce opioid consumption, this also provides useful information regarding analgesic options for patients undergoing TSA. This study can also provide valuable information about the cost-benefit analysis of liposomal bupivacaine versus our institutional standard of care.

References:

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Citations added

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Informed Consent for Research:

(Please see attached document)

Medication Diary:

(Please see attached document)

Morphine Milligram Equivalent Reference:

https://www.cms.gov/Medicare/Prescription-Drug-

Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf

Questionnaires:

PACU discharge questionnaire:

1. *On the pain scale from 0 to 10 where 0 is no pain and 10 is the worst pain you can imagine, how would you rate your current pain?*
   Response: _____
2. *Are you experiencing any discomfort? And if so, where, and how would you describe the discomfort?*
   Response: _____
3. *On a scale from 0 to 10 with 0 being not distressing at all and 10 being very distressing, following your surgery, how distressing do you find the numbness of your arm to be?*
   Response: _____

POD #1 morning in-hospital questionnaire:

1. *On the pain scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what is the **HIGHEST** level of pain that you experienced since leaving the recovery room?*
   Response: _____
2. *On the pain scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what is the **LOWEST** level of pain that you experienced since leaving the recovery room?*
   Response: _____
3. *On the pain scalefrom 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what is the **AVERAGE** level of pain that you experienced since leaving the recovery room?*
   Response: _____
4. *Have you noticed your nerve block starting to wear off, and if so, do you recall the time that it started wearingoff?*
   Response: _____

Prompt for POD #2 phone call questionnaire:

Hello, this is_____calling from the Hartford Hospital Bone and Joint Institute. I am calling regarding the research study on the nerve block you had for your shoulder surgery. I have a few questions to ask you. These questions should take approximately 5 minutes to answer. If you have your medication diary available, please get it as it will help in answering some of these questions.

1. *For the day following your surgery, yesterday, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the highest level of pain that you experienced?*
   Response:_____
2. *For the day following your surgery, yesterday, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the lowest level of pain that you*

experienced?

Response:_____

3. *For the day following your surgery, yesterday, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the average level of pain that you experienced?*

   Response:_____

4. *For the day following your surgery, yesterday, which pain medications did you take and how many did you take. Please reference your medication diary.*

   Response: _____

5. *On a scale from 0 to 10 with 0 being not distressing at all and 10 being very distressing, following your surgery, how distressing did you find the numbness of your arm to be?*

   Response: _____

6. *Following your surgery, have you experienced any of the following? Rash, swelling, or inflammation at the site of the nerve block, bruising at the site of the nerve block, bleeding at the site of the nerve block, ringing in your ears, numbness or tingling of your lips, or nausea and/or vomiting. Additionally, have you had to go to the emergency department at all since leaving the hospital, and if so, what did you go to the emergency department for?*

   Response: _____

7. *If you did not already notice your nerve block wearing off when we saw you on the last the day after your surgery, have you since noticed your nerve block starting to wear off, and if so, do you recall the time that it started wearing off?*

   Response: _____

These are all the questions I have for you today. We will be calling you again in 2 days to ask you some more questions regarding your nerve block. Thank you so much for your time answering these questions. Thank you and have a great day.

Prompt for POD #4 phone call questionnaire:

Hello, this is_____calling from the Hartford Hospital Bone and Joint Institute. I am calling regarding the research study on the nerve block you had for your shoulder surgery. I have a few more questions to ask you. There are a few more questions to answer compared to the previous time we called 2 days ago, however these questions should still only take approximately 5 minutes to answer. If you have your medication diary available, please get it as it will help in answering some of these questions.

1. *For the second day after your surgery, **2 days ago**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the highest level of pain that you experienced?*

   Response: _____

2. *For the second day after your surgery, **2 days ago**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the lowest level of pain that you experienced?*

   Response: _____

3. *For the second day after your surgery, **2 days ago**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the average level of pain that you*

experienced?

Response: _____

4. *For the second day after your surgery, **2 days ago**, which pain medications did you take and how many did you take. Please reference your medication diary.*

   Response: _____

5. *For the third day after your surgery, **yesterday**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the highest level of pain that you experienced?*

   Response: _____

6. *For the third day after your surgery, **yesterday**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the lowest level of pain that you experienced?*

   Response: _____

7. *For the third day after your surgery, **yesterday**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the average level of pain that you experienced?*

   Response: _____

8. *For the third day after your surgery, **yesterday**, which pain medications did you take and how many did you take. Please reference your medication diary.*

   Response: _____

9. *Since your last phone call from us 2 days ago, have you experienced any of the following? Rash, swelling, or inflammation at the site of the nerve block, bruising at the site of the nerve block, bleeding at the site of the nerve block, ringing in your ears, numbness or tingling of your lips, or nausea and/or vomiting. Additionally, have you had to go to the emergency department at all since leaving the hospital, and if so, what did you go to the emergency department for?*

   Response: _____

10. *If you did not already noticed your nerve block wearing off since we called you 2 days ago, have you since noticed your nerve block starting to wear off, and if so, do you recall the time that it started wearing off?*

    Response: _____

11. *On a scale from 0 to 10 with 0 being completely dissatisfied and 10 being completely satisfied, how satisfied are you with your overall pain control after surgery?*

    Response: _____

Thank you again for answering these questions. Please remember to place your medication diary in the pre-addressed and stamped envelope provided to you and mail it back to the hospital as soon as you can. Thank you again for answering these questions and participating in the research study. Will be calling you in approximately 2 months to see how you have been. Have a great day.

Prompt for POD #60 phone call questionnaire:

Hello, this is_____calling from the Hartford Hospital Bone and Joint Institute. I am calling regarding the research study on the nerve block you had for your shoulder surgery. I have a few more questions to

ask you. These questions should still only take approximately 5 minutes to answer.

1. *On the shoulder on which you had surgery **2 months ago,** on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the highest level of pain that youexperienced?*
   Response: _____
2. *On the shoulder on which you had surgery **2 months ago**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the lowest level of pain that youexperienced?*
   Response: _____
3. *On the shoulder on which you had surgery **2 months ago**, on a scale from 0 to 10 with 0 being no pain at all and 10 being the worst pain you can imagine, what was the average level of pain that youexperienced?*
   Response: _____
4. *"How well are you doing with your recovery compared to what you expected on a scale of 0-10 with 10 being the best score and 1 being the worst score."*
   Response: _____
5. *Are you currently taking pain medications for pain in the shoulder that was operated on 2 months ago? Which medications are you taking? How many are you taking?*
   Response: _____
6. *Since your last phone call from us 2 months ago, have you experienced any of the following? Rash, swelling, or inflammation at the site of the nerve block, bruising at the site of the nerve block, bleeding at the site of the nerve block, ringing in your ears, numbness or tingling of your lips, or nausea and/or vomiting. Additionally, have you had to go to the emergency department at all since leaving the hospital, and if so, what did you go to the emergency department for?*
   Response: _____
7. *Has the arm that received the nerve block and surgery returned to normal sensation?*
   Response: _____
8. *On a scale from 0 to 10 with 0 being completely dissatisfied and 10 being completely satisfied, how satisfied are you with your overall pain control after surgery?*
   Response: _____

Thank you again for answering these questions and participating in the research study. Have a great day.