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# LIPOSOMAL BUPIVACAINE PLUS BUPIVACAINE VERSUS BUPIVACAINE HCL FOR INTERSCALENE BRACHIAL PLEXUS BLOCK IN PATIENTS UNDERGOING TOTAL SHOULDER ARTHROPLASTY

A phase IV, randomized, single-blind, single-center study that measures the effects of interscalene brachial plexus blocks (ISB) containing Liposomal Bupivacaine plus 0.5% bupivacaine HCL versus 0.5% Bupivacaine HCL on postoperative pain and opioid utilization in participants who undergo primary total shoulder arthroplasty surgery.

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| **NYULMC Study Number:** | 18-01183 |
| **Study Product:** | Liposomal Bupivacaine (Exparel®) |
| **ClinicalTrials.gov Number** | NCT03913091 |

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**Amended: 7/17/2019**

# Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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## Table of Contents

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# List of Abbreviations

| | |
|---|---|
| ASA | American Society of Anesthesiologist Score |
| VAS | Visual analog scale |
| TSA | Total Shoulder Arthroplasty |
| ISB | Interscalene Nerve Block |
| DVT | Deep vein thrombosis |
| ER | Emergency room |
| AE | Adverse event |
| SAE | Serious adverse event |
| IV | Intravenous |
| PO | Taken orally |
| PRN | Taken as needed |
| TID | Taken three times per day |
| Q4h | Taken every four hours |
| CI | Confidence interval |
| SD | Standard deviation; a parameter, which characterizes a population distribution |
| SE | Standard error |
| ANOVA | Analysis of variance; a linear model |
| NSAID | Non-steroidal anti-inflammatory drug |

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# Protocol Summary

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| Title | Liposomal Bupivacaine (Exparel®) Plus 0.5% Bupivacaine HCL versus 0.5 % Bupivacaine HCL for Interscalene Nerve Block (ISB) for patients undergoing Total Shoulder Arthroplasty (TSA) |
| Short Title | Understanding the effects of Exparel® on post-operative pain management and opioid utilization for patients undergoing TSA |
| Brief Summary | This is a phase IV, randomized, single-blind, single-center study comparing patient related outcomes such as postoperative pain and opioid usage for patients who receive ISB's containing liposomal bupivacaine (Exparel®) plus 0.5% bupivacaine HCL versus 0.5% bupivacaine HCL undergoing total shoulder arthroplasty. |
| Phase | Clinical study phase IV |
| Objectives | To compare opioid utilization and pain management of patients who receive Exparel in an ISB vs standard 0.5% bupivacaine HCL during the initial 72-hour post-operative period. Additionally, to understand the duration of block after addition of Exparel® to bupivacaine in an Interscalene block after TSA |
| Methodology | phase IV, randomized, single-blind, single-center study |
| Endpoint | **Primary Endpoints:**<br>Opioid utilization expressed as (oral morphine mg equivalents) during the initial 72-hour post-operative period.<br><br>**Secondary Endpoints:**<br>Duration of opioid use<br>Patient reported pain scores (VAS)<br>Length of stay<br>Reported long-term narcotic use at home<br>Documented opioid refills<br>Adverse events such as respiratory depression, hypoventilation, reintubation, nausea, constipation |
| Study Duration | 3 years |
| Participant Duration | Four weeks |
| Duration of IP administration | Once during surgery |
| Population | 184 participants scheduled for total shoulder arthroplasty (TSA) |
| Study Sites | NYU Langone Orthopedic Hospital |
| Number of participants | 184 |
| Description of Study Agent/Procedure | Injection of 20mL 0.5% Bupivacaine HCL versus 10mL Liposomal Bupivacaine plus 10mL Bupivacaine 0.5% in an Interscalene block for TSA |
| Reference Therapy | Reference is Bupivacaine 0.5% for Interscalene block |
| Key Procedures | Interscalene nerve block with Liposomal Bupivacaine + Bupivacaine 0.5% |
| Statistical Analysis | Intention-to-treat analysis will be performed with mean, t-tests, within and between group ANOVA and linear regression, |

# 1 Key Roles

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# 2 Background and Specific Aims

With the growing elderly population, the number of total shoulder arthroplasty (TSA) surgeries is increasing. Nationwide, the total and partial shoulder replacements increased from about 18,000 in 2000 to over 45,000 in 2013 according to the American Academy of Orthopedic surgeons (AAOS). One of the greatest drivers of cost following TSA has been shown to be discharge disposition. Effective pain control after surgery is paramount because it facilitates rehabilitation and decreases hospital length of stay. Additionally, it may increase the likelihood of patients being discharged to their home rather than a rehabilitation or skilled nursing facility.

TSA is a procedure that is well confined within the dermatomal distribution of an interscalene brachial plexus nerve block (ISB), making it an ideal procedure to both evaluate and compare the regional potential of varying agents. Although the analgesic coverage is typically ideal, single shot injection of the long acting

local anesthetics, such as Bupivacaine, is limited in duration to the first postoperative day. Conversely, while interscalene perineural catheters offer the ability to continuously provide analgesia, they are time consuming to place, require daily maintenance, and often dislodge or migrate from the desired position. These limitations make interscalene perineural catheters problematic. In order to offer the longevity of an appropriately positioned catheter while preserving the simplicity of a single injection nerve blockade, this group proposes to evaluate the efficacy of liposomal bupivacaine or Exparel® in the setting of TSA.

Exparel® is a sterile, nonpyrogenic, preservative-free liposomal formulation of bupivacaine that provides a non-opioid option for postoperative pain control for up to 72 hours with single shot injection into the perineural space. The chemical and pharmacological nature of Exparel® allows for the encapsulated Bupivacaine to extend its duration of local anesthetic action by delaying medication release as compared to the injection of plain Bupivacaine. The FDA has recently approved Exparel® in its use for shoulder surgery via the interscalene nerve block. Exparel® has shown great potential with both its analgesic benefits and side effect profile; however, adequately powered trials are still necessary in order to compare its benefits to that of standard Bupivacaine.

To date, only one study has been published comparing bupivacaine alone to bupivacaine plus liposomal bupivacaine (1). In that study, the reduction in pain scores was minimal. However, there are several methodological issues with that study: 0.25% bupivacaine was used rather than 0.5%, resulting in a nerve block that was less dense, and making it mandatory to use general anesthesia; the study was probably underpowered; and analgesic use was not quantified.

## 2.1 Specific Aims

**AIM 1:** To determine if Liposomal bupivacaine added to 0.5 % bupivacaine HCL in the interscalene nerve block during TSA surgery significantly changes post-operative opioid usage during the initial 72 hours post-operative period. This will be evaluated by randomizing patients to either receive 0.5% Bupivacaine HCL or Bupivacaine 0.5% with Liposomal bupivacaine in the interscalene nerve block. Opioid consumption will be evaluated in the immediate post-operative period, up to 72 hours post op and for up to 4 weeks after surgery.

**AIM 2:** To determine if the addition of Liposomal bupivacaine to Bupivacaine 0.5% in an interscalene nerve block prolongs post-operative nerve block and hence reduces post-operative pain from during the initial 72 hour post-operative period. Using the same groups as above, the patient stated duration of block (record time of onset of pain) and post-operative VAS Pain scores will be recorded in both the hospital and outpatient settings. Physical therapy endpoints will also be monitored and recorded.

## 2.1 Statistical Hypotheses

We hypothesize that adding Liposomal bupivacaine to Bupivacaine 0.5% for the interscalene nerve block prior to TSA surgery will prolong the sensory block and reduce post-operative pain and opioid usage not only during the patients' inpatient hospital stay but also after discharge from the hospital for up to 72 hours. Furthermore, combining Liposomal bupivacaine and Bupivacaine will reduce complications associated with opioids such as constipation, nausea, pruritus, ileus and opioid dependency. Failing to reject the null hypothesis would signify that Exparel® has no clinically relevant impact on post-operative outcomes in TSA surgery as compared to plain Bupivacaine.

## 2.2 Objectives and Purpose

The goal of this study is to determine the effectiveness of Liposomal bupivacaine at reducing opioid consumption from 24-72 hours when used along with Bupivacaine 0.5% for single shot ISB for total shoulder arthroplasty. In addition, we would also like to determine if Liposomal bupivacaine is effective at prolonging the sensory block and reducing post-operative pain in patients after TSA surgery. We would also

like to determine how reduction in post-operative pain impacts a patient's hospital stay in the short term. Primary outcomes measures will be opioid utilization (in morphine milligram equivalents [MME]) during a 72-hour post-operative period. Secondary outcomes include patient reported pain scores, VAS. While it is expected that the greatest benefit of Liposomal bupivacaine plus Bupivacaine 0.5% will be seen within 24-72 hours after surgery, it is possible that there will be in an overall reduction in long-term opioid use (up to 4 weeks). Secondarily, function/rehabilitation, length of stay, and complications may be impacted by combined use of Liposomal bupivacaine plus Bupivacaine 0.5%.

# 3 Study Design and Endpoints

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| ARM 1: Experimental | Sample Size: 92 | 10 mL Bupivacaine 0.5% + 10 mL Liposomal Bupivacaine |
| ARM 2: Control | Sample Size: 92 | 20 mL Bupivacaine 0.5% |

## 3.1 Description of Study Design

**PRE-SCREENING PHASE/CONSENTING PHASE:**
Surgeons will inform eligible patients of the study during their pre-surgical visit in their office. The surgeons will use an IRB-approved recruitment flyer to help explain the study to the eligible patient. If the patient is agreeable, a member of the research team will provide further details and ask the patient to participate on day of surgery. Informed consent will be obtained on DOS when the patient is in the pre-operative holding room by an authorized research member.

**BASELINE ASSESSMENTS:**
After informed consent has been obtained, participants will complete a total of 3 PROMIS assessments (Upper Extremities, Pain Intensity and Global Physical Health) before undergoing their TSA surgery.

**RANDOMIZATION PHASE:**
Subjects scheduled to undergo TSA will be randomized to either the Bupivacaine 0.5% plus Liposomal bupivacaine Or Bupivacaine 0.5% group. Randomization of each subject will be done on day of surgery using randomization.com software to generate the assignment.

**TREATMENT PHASE:**
Subjects in the Bupivacaine plus Liposomal bupivacaine group will receive an interscalene nerve block with 10mL 0.5% Bupivacaine and 10mL of Liposomal bupivacaine. The control group will receive an interscalene nerve block with 20mL 0.5% Bupivacaine HCL. The anesthesiologist will NOT be blinded to what solution is being injected, as liposomal bupivacaine is a white fluid while bupivacaine is clear. All other stakeholders (patient, surgeon, other caregivers, and research staff collecting the data) will be blinded to the patient's group assignment.

**POST-OPERATIVE PHASE:**
After initial recruitment, subjects' pain will be assessed via visual analog scale (VAS) by nursing staff during the post-operative period as per standard of care. The VAS pain scores are collected and documented in the patient's electronic medical record. Additionally, a standardized regimen of pain medication will be given to all subjects who are enrolled. The pain medications given to patients are standard of care medications and vary based on pain level. The clinical staff determines this for each patient.

Occupational and physical therapy progress and activity goals will be reviewed. As per standard of care, motor testing of the operated shoulder and arm will be assessed during these visits. This includes: No weight bearing exercises will be performed as per surgeon's instructions and the nursing staff will continue to obtain VAS pain scores.

During the 24-72 hour post-operative period, research staff will visit the patient while they are in the hospital to obtain and verify the pain medication taken. If the patient is discharged before the 72-hour period, the research staff will give the patient a copy of a medication record diary to complete. Additionally, the staff member will call the patient within 1-2 business days to obtain the remaining opioid utilization information.

After discharge, the research staff will continue to follow up with the patient on POD 7, POD 14 and POD 30 to assess pain scores, opioid usage patterns, and functional status. The pain intensity PROMIS assessment will be administered during each phone call. Additionally, on POD 30, participants will complete the Upper Extremity PROMIS form. Research staff will verify documented opioid refills through Epic and pharmacy records.

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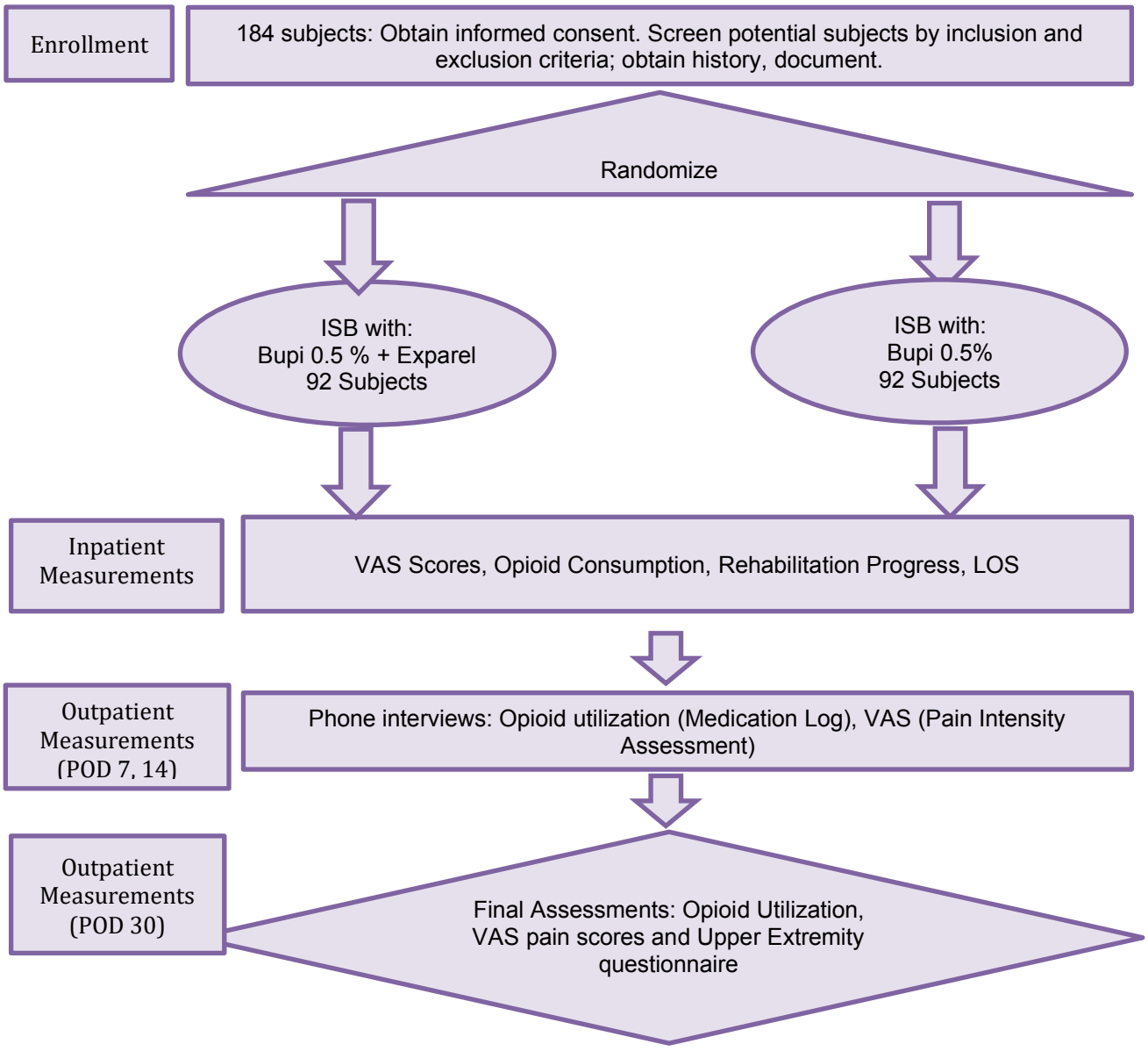
## 3.2 Schematic of Study Design



# 4 Study Enrollment and Withdrawal

The researchers will approach patients scheduled for primary total shoulder arthroscopy who are eligible for participation in the study. Anesthesiology attendings, fellows, residents and authorized researchers will consent and enroll patients pre-operatively.

## 4.1 Inclusion Criteria

1. Patients between 18 and 85 years of age
2. Patients undergoing total shoulder arthroplasty; and
3. Patients who consent to be randomized.

## 4.2 Exclusion Criteria

1. Patients younger than 18 and older than 85;
2. Patients with a history of chronic pain that have used opioids for pain management for 3 months or longer;
3. Patients who are allergic to oxycodone;
4. Patients who are unable to speak English;
5. Patients with diagnosed or self-reported cognitive dysfunction;
6. Patients with a history of neurologic disorder that can interfere with pain sensation;
7. Patients with a history of drug or recorded alcohol abuse;
8. Patients who are unable to understand or follow instructions;
9. Patients with severe liver disease, renal insufficiency, congestive heart failure, and/or significant heart disease;
10. Patients with an allergy or contraindication to any of the medications used in the study, or patients with a contraindication to any study procedures;
11. Patients with BMI over 40;
12. Any patient that the investigators feel cannot comply with all study related procedures;
13. NYU Langone Health students, residents, faculty or staff members

## 4.3 Vulnerable Subjects

No vulnerable populations will be intentionally solicited. It is possible that employees, economically disadvantaged persons and students will be solicited in the course of enrollment however no one will be specifically recruited for these reasons and no one with ties to the NYU Anesthesiology and Orthopedics department or NYU School of Medicine will be eligible for participation.

## 4.4 Recruitment and Consent

This study will utilize EPIC to identify subjects and use Redcap in addition to the firewall protected shared drive to manage and store relevant data.

**Process of Consent**

The consent for participation will be obtained on day of surgery in pre-operative holding room by the regional anesthesiology fellow, Attending Physician, or authorized researcher. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation suited to their comprehension of the purposes, procedures, potential risks and their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed

informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be given to the patient, placed in the patient's electronic medical record and the original copy will be stored in the research regulatory binder. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

**Subject Capacity**
All subjects will be assessed for capacity to give informed consent. Capacity will be assessed through the subjects' ability to express understanding of the information presented to them, their ability to express a choice, their appreciation of how this is relevant to them, and reasoning about how the study might impact them and others.

**Subject/Representative Comprehension**
The subject themselves will have to clearly state back the basic goals of the study (i.e. to look at the effect of different local anesthetics on post op pain after total shoulder replacement surgery) and state that they are willing to participate. This may be done in English or in their primary language with an interpreter.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research coordinator, Randy Cuevas at 212-598-6085.

## 4.5 Duration of Study Participation

While the study will be open for 3 years after beginning enrollment, the actual length of a study subject's participation is four weeks.

## 4.6 Total Number of Participants and Sites

Recruitment will end when approximately 184 participants are enrolled. It is expected that approximately 184 participants will be enrolled in order to produce 146 evaluable participants. The only site for enrollment will be the NYU Langone Orthopedic Hospital.

## 4.7 Participant Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

## 4.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:
1. Determination of unexpected, significant, or unacceptable risk to participants;
2. Demonstration of efficacy that would warrant stopping;

3. Insufficient compliance to protocol requirements;
4. Data that are not sufficiently complete and/or evaluable; or
5. Determination of futility

# 5 Risks and Benefits

## 5.1 Potential Risks

Bupivacaine used for this study is the standard of care for ISB. Liposomal Bupivacaine (EXPAREL®), a second study drug, has recently been approved by the FDA for use in interscalene blocks.

The potential risks associated with bupivacaine include neurologic and cardiac toxicity, if injected intravascularly. However, the risk is very low because a trained anesthesiologist using ultrasound guidance will perform the nerve block. This allows the anesthesiologist to see and avoid blood vessels when administering the medication. Additionally, the syringe of the local anesthetic will be aspirated prior to injection to ensure that the block needle tip is not intravascular.

The use of Liposomal Bupivacaine or Exparel® in this study is experimental and may cause side effects. Exparel® has recently been approved by the FDA to be used in interscalene blocks. The potential risks associated with Exparel® include nausea, constipation, and fever. In addition, there can be temporary sensory and motor loss, depending on the dosage, site of injection and duration of the nerve block. However, the amount (10mL) used in this study meets FDA dosage-regulations for this medication.

## Potential Benefits

Study subjects may experience better pain control, improved satisfaction, decreased need for opioids and reduced incidence of side effects. If the study is not inconclusive, the study's results may benefit future patients by showcasing that Liposomal Bupivacaine improves pain control beyond 24hours in an ISB. Additionally, advocate for the use of Liposomal Bupivacaine as the standard of care for peri- and postoperative pain control in future patients undergoing TSA.

# 6 Statistical Analysis

## 6.1 General Approach

Intention-to treat. The primary analysis will follow the intention-to-treat (ITT) principle in order to evaluate the true outcome of the intervention as experienced by the patient who is blinded to the intervention.

Missing Data. It is anticipated that the data for some subjects will be incomplete for various reasons: missing daily-diary entries, refusal to answer a sensitive question on a questionnaire, onset of illness, loss-to-follow-up, etc. All occurrences of incomplete data will be investigated to carefully document the reasons for the missing data. If the primary outcome (amount of opioid used between 24 and 72 hours after surgery) cannot be ascertained with a reasonable degree of certainty, the patient will be excluded from the study.

## 6.2 Analysis of Endpoints

**Primary Endpoints:**
Opioid utilization (expressed as oral morphine mg equivalents) used during initial 24-72 hours post-operative period after surgery.

**Secondary Endpoints:**

Duration of opioid use
Patient reported pain scores (VAS)
Length of stay
Progress with physical therapy
Reported long-term narcotic use at home
Discharge location: home, acute rehab or skilled nursing facility
Documented opioid refills
Adverse events such as respiratory depression, hypoventilation, reintubation, nausea, constipation

The analysis of opioid use, VAS, and PROMIS assessments will rely on a univariate analysis of variance model for mean score. This model is in the class of models commonly known as unirep-ANOVA models. It assumes that the mean score is a function of elapsed time and the treatment regimen assigned. This model considers the fact that the subject's repeated measures are correlated. The fitted model will provide statistical estimates of the mean levels, the treatment-effect differences between mean levels, the standard deviation, the intra-class correlation coefficient, 95% CIs, standard errors (SE), and statistical hypothesis tests. The estimates of means will be used to compute summary criteria such as area under the curve (AUC) for each regimen. All estimates reported will be presented their 95% CIs.

All endpoints will be evaluated as fits the data set with graphical figures such as scatter plots, box-and-whisker plots, and frequency histograms to visualize the distribution of these outcomes and their relationships to covariates and treatment assignment. When appropriate descriptive graphical and tabular methods will also be estimated and presented in a graphical figure.

### 6.2.1 Baseline Descriptive Statistics

The following patient data will be recorded: age, gender, height, weight, date of admission, date of discharge, laterality, surgical approach, implants used, duration of surgery, contamination, ASA, comorbidities (smoking, cardiac history, diabetes etc.), CBC (WBC, PCV, HGB, RBC, indices, platelet count, differential), and medications. All of this information will be accessible in the patient's medical record.

## 6.3 Sample Size

184 subjects will be enrolled

## 6.4 Enrollment/Randomization/Masking Procedures

We will utilize randomization.com to generate a randomization assignment for all 184 participants. Someone that is not a stakeholder in the study will make randomization envelopes, which include the study ID number, the treatment assignment, and dosage specifics. These randomization envelopes will then be distributed to the anesthesiologist pre-operatively by the authorized researcher after informed consent is obtained.

## 6.5 Breaking the Study Blind/Participant Code

If there is any adverse event related to the drug, we will break the blind for the subject and randomization will be disclosed to the patient.

# 7 Assessment of Safety

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal

- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

## 7.1 Definition of Serious Adverse Events (SAE)

**Serious Adverse Event**

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious will be regarded as **non-serious adverse events**.

## 7.2 Classification of an Adverse Event

### 7.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

1. **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2. **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

### 7.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs must have their relationship to study agent assessed. For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

1. **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals.
2. **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable

time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal).

3. **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
4. **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
5. **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Dr. Umeh will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

## 7.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events will be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

### 7.4 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

## 8 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries will be printed legibly in black ink.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

## 9 Ethics/Protection of Human Subjects

### 9.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

### 9.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

### 9.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

# 10 Data Handling and Record Keeping

## 10.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Redcap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

## 10.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug

for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

## 10.3 Protocol Deviations

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

Protocol deviations will be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

## 10.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of the research. This trial will be registered with clinicaltrials.gov as per the ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007.

## 10.5 Data Safety and Monitoring

The definition of unanticipated problems (UP) involving risk to subjects or others according to the NYU SOM IRB Drug Trial Protocol template is any incident, experience or outcome that meets all of the following criteria: unexpected in nature, severity or frequency, related or possibly related to participation in the research, suggests that the research places subjects or others at greater risk of harm. The definition of an adverse drug event according to the NYU SOM IRB Drug Trial Protocol is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study.

The DSMB will be made up of the Principal Investigator– Uchenna Umeh M.D. and Co-investigators- Arthur Atchabahian M.D. and Mandeep Virk M.D. All members of the DSMB are board certified physicians in their respective specialties.

The DSMB will review safety data after the first five enrolled subjects and every three months thereafter. All unanticipated problems that increase risk to the subjects will be reported to the IRB per NYUSOM IRB policy. The time frame for reporting SAE and UP to the DSMB is by telephone within 24 hours of awareness of the event. The time frame for reporting SAE and UP to the IRB is to submit reports promptly but no later than 5 working days from the time the investigator becomes aware of the event.

During these meetings, the DSMB will review and analyze any unanticipated problems or adverse events involving risk to the patient including any neurological damage, significant delay in physical therapy progress, local anesthetic toxicity or allergic reaction to Exparel etc.

Specific study stopping points is the occurrence of a serious adverse event such as a severe allergic reaction to Exparel. Additionally, after 5 patients in each group have completed all study related procedures, a brief safety analysis will be done by the Principal Investigator, Uchenna Umeh M.D., to check for evidence of systemic local anesthetic toxicity. Events will be reported to the anesthesia department QA.

**Additionally, the DSMB will perform an interim safety and data analysis after 50 patients have completed all study related visits.**

# 11 Study Finances

## 11.1 Funding Source

Both Anesthesiology and Orthopedic Surgery will use departmental funds to provide the Exparel used for this study.

## 11.2 Costs to the Participant

There are no expected costs to the subjects.

## 11.3 Participant Reimbursements or Payments

Participants will not receive any financial compensation for participation in this study.

# 12 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

# 13 References

1. Vandepitte C, Kuroda M, Witvrouw R, et al. Addition of Liposome Bupivacaine to Bupivacaine HCL Alone for Interscalene Brachial Plexus block in Patients Having Major Shoulder Surgery. *Reg Anesth Pain Med.* 2017;42(3):334-341.
2. Ilfeld BM, Viscusi ER, Hadzic A, et al.Safety and side effect profile of liposomal bupivacaine (Exparel) in peripheral nerve blocks. *Reg Anesth Pain Med.* 2015;40:572-582
3. Ilfeld BM, Malhotra N, Furnish TJ, Donahue MC, Madison SJ. Liposomal bupivacaine as a single-injection as a single-injection peripheral nerve block: a dose-response study. *Anesth Analg*. 2013;117:1248–1256.
4. Chahar P, Cummings KC 3rd. Liposomal Bupivacaine: a review of a new bupivacaine formulation. *J Pain Res.* 2012;5:257–264.
5. Hadzic A, Minkowitz HS, Melson TI, et al. Liposomal Bupivacaine femoral nerve block for post surgical analgesia after total knee arthroplasty. *Anesthesiology.* 2016;124:1372–1383.

# 14 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

## 14.1 Opioid Equivalents

**Notes from Lamplot (2013)**

| Opioid and Route | Dose (mg) | Conversion Factor |
|---|---|---|
| Morphine IM/IV | 10 | 1.0 |
| Hydromorphone IM/IV | 1.67 | 6.0 |
| Hydrocodone oral | 30 | 0.3 |
| Tramadol oral | 100 | 0.1 |
| Oxycodone oral | 20 | 0.5 |
| Vicodin 5/500 oral | 6 tabs | 1.7 |

**Equianalgesic Doses of Opioids**[28]

| Opioid | Oral Equianalgesic Dose (mg) |
|---|---|
| Buprenorphine | 0.3 |
| Oxymorphone | 1.5 |
| Butorphanol | 2 |
| Hydromorphone | 2 |
| Oxycodone | 7 |
| Hydrocodone | 10 |
| Morphine | 10 |
| Methadone | 10-20 |
| Tramadol | 40 |
| Propoxyphene | 43-45 |
| Codeine | 80 |
| Meperidine | 100 |

## 14.2 PROMIS Assessments

Upper Extremities Short Form (Administered Pre-Operatively in Holding Area):

PROMIS® Item Bank v2.0 – Physical Function – Short Form 7a

### Upper Extremity – Short Form 7a

**Please respond to each question or statement by marking one box per row.**

| | | Without any difficulty | With a little difficulty | With some difficulty | With much difficulty | Unable to do |
|---|---|---|---|---|---|---|
| PFA14r1 | Are you able to carry a heavy object (over 10 pounds /5 kg)? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA34 | Are you able to wash your back? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA36 | Are you able to put on and take off a coat or jacket? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFB13 | Are you able to carry a shopping bag or briefcase? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFB28r1 | Are you able to lift 10 pounds (5 kg) above your shoulder? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFB34 | Are you able to change a light bulb overhead? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFM16 | Are you able to pass a 20-pound (10 kg) turkey or ham to other people at the table? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |

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Global Health Short Form (Baseline Assessment)

PROMIS Scale v1.2 – Global Health Physical 2a

## Global Health – Physical 2a

**Please respond to each question or statement by marking one box per row.**

| | | Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|---|---|
| Global03 | In general, how would you rate your physical health? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Completely** | **Mostly** | **Moderately** | **A little** | **Not at all** |
| Global06 | To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair? | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |

Pain Intensity Scores:

PROMIS Item Bank v.1.0 – Pain Intensity – Scale

## Pain Intensity – Scale

**Please respond to each item by marking one box per row.**

| | **In the past 7 days…** | **Had no pain** | **Mild** | **Moderate** | **Severe** | **Very severe** |
|---|---|---|---|---|---|---|
| PAINQU6 | How intense was your pain at its worst? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| PAINQU8 | How intense was your average pain? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| | | **No pain** | **Mild** | **Moderate** | **Severe** | **Very severe** |
| PAINQU21 | What is your level of pain right now? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

## 14.3 Medication Usage Record

### Medication Record for TSA Surgery

Thank you for participating in our research study and helping us improve pain control for patients undergoing total shoulder arthroplasty (TSA) surgery.

**Patient**: _____

Pain medication: **Percocet**

Please record the following information in the log below:

1. Time when you take your pain medication
2. How many pills you took at each time
3. Pain score on a scale of 0-10 (0 being no pain and 10 being the worst pain imaginable)
4. Any additional pain medications (such as Advil), therapies (such as ice packs) and side effects (such as itching or nausea).

| Time | Number of pills of Percocet | Pain Score (scale of 0-10) | Additional pain medications, therapy or side effects |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

We will call you within 1-2 business days after surgery to ask for the above information. Additionally, participants can also scan, photograph and email the medication record to Randy Cuevas at Randy.Cuevas@nyulangone.org

Thank you for your participation.