Obstetric Liposomal Bupivacaine Via Surgical Transversus Abdominis Plane Block for Post Cesarean Pain Control: a Single-blind Pilot Randomized Controlled Trial

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PI: Kathleen Antony, MD, MSCI

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Obstetric Liposomal Bupivacaine via Surgical Transversus Abdominus Plane Block for Post Cesarean Pain Control: a single-blind pilot randomized controlled trial

The OBstetric Liposomal Bupivacaine Trial (ObLiBupi Trial)

Protocol Number: UnityPoint Health-Meriter IRB#: 2021-005

Principal Investigator: Kathleen M. Antony, MD, MSCI

Protocol Version History

Protocol Version	Version Date	Brief description of protocol modification/actions requested, if any
Version 1.7	*06/20/2021*	***Do not update version # until final draft***

Table of Contents

1. Statement of Compliance

The signature below constitutes that the research will be conducted in accordance with the approved protocol, applicable regulations, guidelines, laws and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

PRINTED OR TYPED NAME	SIGNATURE	DATE
Principal Investigator		

2. List of Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
CFR	Code of Federal regulations
CLIA	Clinical Laboratory Improvement Amendments
CoC	Certificate of Confidentiality
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data & Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
HER	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH E6	International Council on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICTR	Institute for Clinical and Translational Research
IRB	Institutional Review Board
MOP	Manual of Procedures
OHRP	Office for Human Research Protections
Ob/Gyn	Department of Obstetrics and Gynecology
PHI	Protected Health Information
PI	Principal Investigator
PRC	Pharmaceutical Research Center
QA	Quality Assurance
QC	Quality Control
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRC	Scientific Review Committee
UP	Unanticipated Problem

3. Study Summary

3.1 Synopsis

Title	*Obstetric Liposomal Bupivacaine via Surgical Transversus Abdominus Plane Block for Post Cesarean Pain Control: Single Blind RCT*
Protocol Number	UnityPoint Health-Meriter IRB#: ***
ClinicalTrials.gov Identifier	ClinicalTrials.gov Identifier: ***
Number of Site(s)	Single center
Main Inclusion Criteria	○ Singleton or multifetal pregnancy ○ Able to receive neuraxial analgesia ○ Planned/ scheduled Cesarean delivery OR non-urgent Cesarean delivery with adequate time to consider and consent to the study

Main Exclusion Criteria	○ Known hypersensitivity to bupivacaine (defined as a history of a reaction or allergy to bupivacaine (injectable, intravenous, or transdermal) reported by patient or documented in the medical record ○ Contraindication to regional analgesia ○ Positive urine drug screen at admission to the hospital, if ordered for clinical purposes. ○ Current opioid use or opioid use disorder per patient report or documented in the medical record ○ Chronic opioid use or opioid use disorder, either patient reported or documented in the medical record, defined as opioid use on most days for >3 months ○ Planned cesarean hysterectomy (excluded due to anticipated blood loss and alternative pain control measures, possible prolonged intubation) ○ Planned vertical midline incision (excluded due to possible different postpartum pain) ○ Presence of renal dysfunction precluding the use of NSAIDs (NSAIDs are part of the usual postpartum pain regimen/ hospital protocol) per discretion of the treating physician or PI ○ Ischemic heart disease, congestive heart failure, or cardiomyopathy of pregnancy precluding the use of NSAIDs (NSAIDs are part of the usual postpartum pain regimen/ hospital protocol) per discretion of the treating physician or PI ○ Significant liver dysfunction precluding the use of acetaminophen (acetaminophen is part of the usual postpartum pain regimen/ hospital protocol) per discretion of the treating physician or PI ○ Coagulopathy ○ Planned discharge from the hospital less than 48 hours postpartum ○ Unable to receive post-operative scheduled acetaminophen for any reason, such as allergy to acetaminophen or elevated liver function tests precluding acetaminophen use ○ Unable to receive post-operative scheduled NSAIDs for any reason, such as allergy to ketorolac or ibuprofen, or renal dysfunction precluding NSAID use ○ **Seizure disorder**: Specifically, poorly controlled seizure disorder defined as having had a seizure within the last three years despite antiepileptic use or poorly managed seizure disorder due to medication non-compliance. ○ **Cardiac disease or arrhythmia**: Defined as ischemic heart disease, peripartum cardiomyopathy, heart failure (with reduced or preserved ejection fraction, compensated or decompensated). Patients with a remote history of non-cyanotic pediatric cardiac surgery (like a VSD closure or PDA ligation as a child) do not need to be excluded. History of adult cardiac surgery without ongoing problems or treatments other than chronic anticoagulation (mitral valve repair for MVP or aortic valve replacement for bicuspid aortic valve for example) would not need to be excluded. History of repaired congenital cyanotic heart disease should be considered for exclusion, ultimately up to the anesthesiologist that day. A patient with a history of arrhythmias not requiring medication or ablation would NOT need to be excluded and could be included in the study. History of ablation or active anti-arrhythmic medication should be considered for exclusion. ○ **Hypoxia:** Defined as requiring supplemental oxygen during the day. ○ **Acidosis.** This will be uncommon in our population, but if someone has active diabetic ketoacidosis will exclude.

Primary Objective	To reduce the total dose of opioids received in the first 48 hours post-op after cesarean delivery. All opioid doses will be converted into oral morphine equivalents for standardization purposes
Study Design	This study will be a single-center, single blind, randomized controlled trial. The study will be conducted at UnityPoint-Health Meriter Hospital under investigators from the University of Wisconsin-Madison. Obstetric patients undergoing scheduled Cesarean delivery at UnityPoint-Health Meriter will be eligible.
Study Intervention	The control arm will receive 30 mL of bupivacaine HCl plus 50 mL of saline injected into the lateral transversus abdominus plane via surgical approach (abdominal approach). The intervention arm will receive 30 mL of bupivacaine HCl plus 30 mL of saline plus 20 mL of liposomal bupivacaine injected into the lateral transversus abdominus plane via surgical approach (abdominal approach).
Total Number of Subjects	60 Subjects
Study Population	Pregnant women undergoing scheduled cesarean delivery
Statistical Methodology	The primary outcome of total opioid dose (in OME) will be compared via Student's t-test or Mann-Whitney U test if the distribution is non-normally distributed, and additional outcomes will be assessed via Student's t-test, Chi-squared, or non-parametric tests, as appropriate. Statistics will be performed by Scott Hetzel.
Estimated Enrollment Period	24 months from initial subject enrollment
Estimated Study Duration	24 months from initial subject enrollment

4. Key Roles

The following is a list of all key personnel and roles:

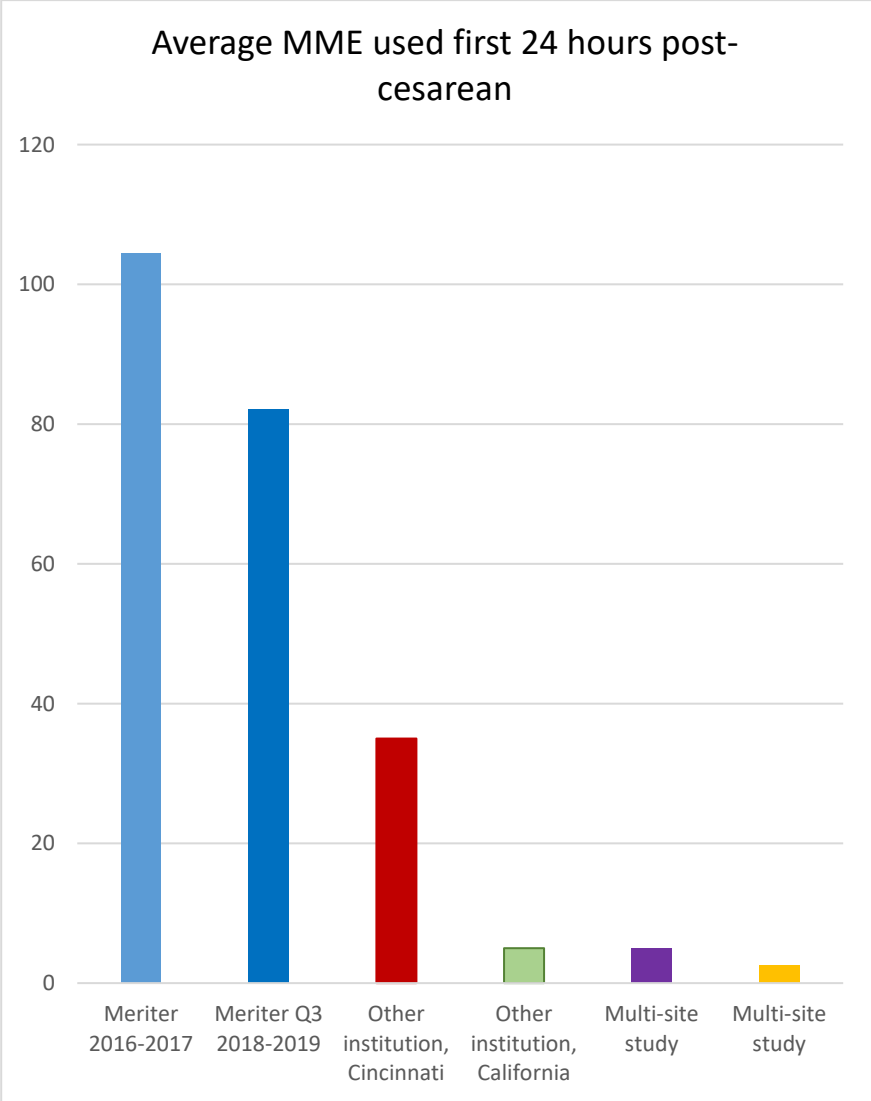
Principal Investigator	Kathleen M. Antony, MD, MSCI Department of Obstetrics & Gynecology Division of Maternal-Fetal Medicine University of Wisconsin School of Medicine and Public Health 1010 Mound Street, 4th Floor, MFM Madison, WI 53715 kantony@wisc.edu Tel: 608-417-6099 Fax: 608-417-4270 UnityPoint Health-Meriter Hospital, Madison, WI
Participating Site(s)	UnityPoint Health, Meriter Hospital 202 S. Park Street, Madison, WI 53715
Co-Investigator(s)	Luther Gaston, MD Division of Academic Specialists in General Obstetrics and Gynecology 1010 Mound Street, 4th Floor, MFM Madison, WI 53715 UnityPoint Health-Meriter Hospital, Madison, WI Ryan McDonald, MD Division of Academic Specialists in General Obstetrics and Gynecology 1010 Mound Street, 4th Floor, MFM Madison, WI 53715 UnityPoint Health-Meriter Hospital, Madison, WI
Medical Monitor	To be determined.
Data and Safety Monitoring Board Contact	To be determined.
Funding Sponsor	Meriter Foundation
Funding Point of Contact	Kathleen M. Antony, MD, MSCI (above) kantony@wisc.edu Lisa Grady lgrady@wisc.edu
Biostatistician	Scott Hetzel, MS Biostatistics and Medical Informatics 207G WARF hetzel@biostat.wisc.edu 608-265-4311

5. Introduction

5.1 Background

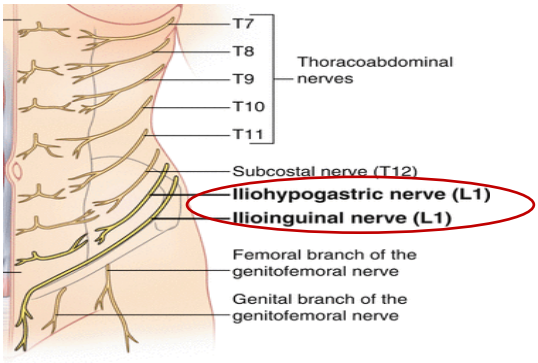
Cesarean birth is the most common major surgical procedure performed in the United States, with rate of about 31.9% of deliveries.(1) Pain management following cesarean birth involves a combination of opioid and non-opioid analgesia. Prescription opioid abuse and dependence has increased rapidly in the United States over the past two decades, with a four-fold increased rate of unintentional overdose using prescription opioids from 2000-2010.(2)

An evaluation by the Centers for Disease Control and Prevention found that many patients become addicted to opioids following treatment of acute pain, including after cesarean delivery.(3,4) Between 1 in every 50 and 1 in every 300 women undergoing cesarean delivery become chronic opioid users.(4,5) If this rate holds true for women delivering at UnityPoint Health-Meriter, between 4 and 27 women delivering at Meriter would potentially become chronic opioid users every year. Women delivering at UnityPoint Health-Meriter also use more opioids in the immediate postpartum period than women delivering elsewhere in this country. During 2016-2017, the per-woman average cumulative oral morphine milligram equivalent (MME) dose in the first 24 hours postpartum for opioid-naive women undergoing cesarean delivery was 104.4 mg. Based upon this high cumulative opioid dose, a standardized analgesia regimen was created in 2018 which prioritized scheduled acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). After this protocol was implemented, the per-woman average cumulative MME dose was reduced to 82.1 mg in the first 24 hours postpartum. While successful at reducing the cumulative MME dose, the dose of 82.1 mg MMEs within the first 24 hours postpartum exceeds the opioid dose used by other institutions with a range of MMEs in the literature of 2.5-35 mg.(6–9)



Efforts to reduce opioid exposure postoperatively may reduce the potential for addiction. There is a nationwide opioid crisis, and the Madison community is no exception; any intervention to decrease future opioid use disorder is of interest to the healthcare community. For the purpose of this protocol, the term “opioids” refers to both natural opiates such as morphine and codeine and synthetic opioids, such as fentanyl. The rate of respiratory events is related to the total opioid dose,(10) so efforts to decrease the total dose may decrease the frequency of such events.

In order to address the high cumulative MME dose received by postpartum women delivering at UnityPoint Health-Meriter Hospital, we have formed a committee to create an enhanced recovery after surgery protocol which is a multimodal approach to pain control. This multipronged approach incorporates patient educational videos and handouts with nursing education and has representatives from nursing, nursing leadership, the obstetrical residency program, pharmacy, the anesthesia department, nutrition, and information technology. We have formed such a group at Meriter aimed at enhancing recovery after cesarean surgery (ERACS) and we are developing an evidence based protocol to achieve these aims.



However, the experience of other institutions has shown that, while these efforts reduce cumulative MME dose, even with these ERACS protocols in place that there is additional benefit to the use of liposomal bupivacaine when administered via transversus abdominus plane (TAP) block. The rationale for additional benefit of bupivacaine via TAP block is because neuraxial morphine (one portion of the ERACS protocol) has effect up to 12-24 hours whereas liposomal bupivacaine has effect up to 72 hours. A TAP block comprises of injection of local anesthesia into the plane between the internal oblique muscle and transversus abdominis muscle in the area of the iliohypogastric and ilioinguinal nerves (Figure).

Liposomal bupivacaine is a long-acting local anesthetic which is FDA approved for single dose infiltration into a surgical site or for nerve blocks. With liposomal bupivacaine, the active drug (bupivacaine) is encapsulated in a liposomal platform and released slowly over the course of days with an approximate 72 hour duration.(11) One prior retrospective study conducted in a center with a fully implemented obstetrical enhanced recovery after surgery protocol already in place found that when they added liposomal bupivacaine administered via transversus abdominus plane (TAP) block, they found a 47% reduction in total post-cesarean opioid consumption, a 46% reduction in pain scores, and a decreased length of hospital stay from 4.3 days to 3.1 days (*P* <0.001).(12) As noted, this center already had implemented intrathecal morphine, scheduled acetaminophen and NSAIDs, and other components that we are aspiring to add to our multimodal enhanced recovery after cesarean protocol. **Thus, the benefit they demonstrated to the liposomal bupivacaine TAP block was in addition to an existing enhanced recovery after surgery protocol.** More recently, a randomized controlled trial utilizing liposomal bupivacaine as the intervention in addition to regular bupivacaine and intrathecal morphine (in both the intervention and control arm) found a 51.6% reduction in opioid use in the first 72 hours after cesarean (P=0.0002) and also found that 54% of women in the intervention arm used less than 15 mg of MME total compared to 24.7% in the control arm (P=0.0012).(9)

TAP plane blocks via the usual anesthesia-administered technique, however, require placement by an anesthesiologist.(13) The anesthesiologist needs specialized training, and ultrasound guidance is required to ensure proper placement.(13) Placement by the anesthesia team with ultrasound guidance carries the risk of complications such as inadvertent peritoneal penetration and bowel injury.(12,14–16) Placement of this block is also more challenging in the setting of obesity,(17) and 60% of the patients undergoing cesarean birth at UnityPoint Health-Meriter have obesity.

Therefore, a surgical, or abdominal, approach to the transversus abdominus plane block has been proposed. In 2011 Owen *et al*. piloted this approach on 16 women undergoing cesarean delivery.(15) They used 0.5% bupivacaine and fentanyl and found their surgical TAP block decreased the average 24 hour MME from 23.4 mg to 14.1 mg and increased the time to the first request for opioid medications.(15) Thus, the surgical approach to TAP block was effective. An RCT then compared surgeon-administered TAP block compared to anesthesiologist-placed TAP block and found no significant differences in opioid consumption or pain scores, therefore, the mode of administration does not appear to impact the efficacy of the block.(14) The RCT

comparing surgeon-administered TAP block to anesthesiologist-administered TAP block also found the time was significantly less for the surgeon-administered TAP block (2.4 minutes versus 12.1 minute, *P* <0.001) and the time spent in the operating room was also significantly lower (55.3 versus 77.9 minutes, *P* <0.001).(14) Finally, the patient satisfaction with pain scores was not different (satisfaction 7.8 with surgical TAP versus 6.7 with conventional TAP, P 0.11).(14) Finally, a study that sought to assess the feasibility of surgical TAP block on a larger scale found that the procedure was safe, easy, and effective and did not require any specialized equipment.(16) So placement of the TAP block via a surgical or abdominal approach by the obstetrical-surgeon is feasible, equally effective, and faster than placement by the anesthesia team. However, the studies demonstrating the effectiveness of this approach used bupivacaine or ropivacaine, both of which have a relatively short duration of action. Additionally, none of these three studies utilized intrathecal (neuraxial) morphine.(14–16)

Intrathecal, or neuraxial, morphine is a long acting spinal anesthetic with efficacy up to 24 hours after spinal injection.(18) The effect of neuraxial morphine would be expected to exceed the effect of regular bupivacaine which has an effect up to 7 hours.(19) Therefore, only liposomal bupivacaine would be expected to have an ongoing effect after the effect of neuraxial morphine has worn off.

There is a strong interest in reducing post-cesarean opioid consumption at our institution. Collaborators in the department of anesthesia, nurses, and the pharmacy are all committed to reducing opioid consumption, particularly given the risk of post-operative respiratory depression related to opioid use. The rate of moderate to severe respiratory compromise at our institution is 184/10,000 deliveries compared to 1.6/10,000 in the general obstetrical population. This is 112-fold higher than reported in the literature.(20) In our population we found the risk of respiratory compromise to be higher among women using more opioids.(20) If successful, this project will decrease post-operative opioid use and may therefore reduce post-operative respiratory morbidity and opioid exposure leading to future addiction. Future efforts will focus on continuing to reduce opioid use in our post-cesarean population.

This study will be conducted in compliance with this protocol, good clinical practice, and under the supervision of the Meriter Institutional Review Board (IRB). The population studied will include pregnant women who are at least 18 years old who are pregnant who will be delivered via cesarean delivery at UnityPoint Health-Meriter Hospital. This study will also not start until the multidisciplinary obstetrical enhanced recovery after cesarean surgery (ERACS) protocol is completed and fully operational and implemented to reduce confounding by pre and post-protocol implementation on patient pain and opioid use.

5.2 Rationale

The current standard of care for post-Cesarean pain control consists of a combination of opioids and non-steroidal anti-inflammatory analgesics, such as ibuprofen. Patients can become addicted to opioids following treatment of acute post-Cesarean pain and are acutely at risk of moderate to severe respiratory compromise.(3,4) The rate of respiratory events is related to the total opioid dose, efforts to decrease the opioid dose may decrease the frequency of such events. (10) Reducing the opioid dose may also reduce the risk of addiction. There are many ongoing completed and ongoing studies nationwide seeking to reduce post-cesarean opioid use, some of which could be integrated into practice once completed.(8)

This study seeks to identify whether the addition of liposomal bupivacaine to regular bupivacaine and saline administered via surgical TAP block will reduce the cumulative opioid dose in the first 48 hours after cesarean. The liposomal bupivacaine and control arm (bupivacaine plus saline) will both also receive the current standard of care, which at UnityPoint Health-Meriter consists of scheduled NSAIDs, acetaminophen, and “rescue” opioids. This study will also be started after the enhanced recovery after cesarean (ERAC) protocol has started and therefore all women will have received intrathecal or neuraxial morphine.

This study is novel in its surgical approach to the TAP block which has not previously been performed in women receiving intrathecal morphine and also is novel in that it will be using liposomal bupivacaine. The average BMI of our cesarean delivery population is also higher than reported in the existing investigations utilizing surgical TAP block, thus while we are not specifically targeting women with obesity, our study will likely include a significant proportion of women with obesity.(14–16)

If successful, this pilot randomized controlled trial will be used to justify a larger randomized controlled trial. The effect size found via this pilot will be used to ensure that the larger randomized controlled trial will be adequately powered. If that second trial successfully demonstrates that surgical TAP block with liposomal bupivacaine indeed reduces post-cesarean opioid use, pain, and length of stay compared to women receiving regular bupivacaine, then a cost-benefit analysis will be performed and it may be considered for more routine use at UnityPoint Health-Meriter and possibly elsewhere.

Bupivacaine is safe to use in the immediate peripartum and postpartum period. However, it does have risks. Bupivacaine is highly potent and lipid soluble and can cause central nervous system toxicity.(11) Giving higher doses of bupivacaine HCl (regular bupivacaine) in hopes of prolonging anesthesia can be harmful.(11) In contrast, liposomal bupivacaine has lower maximum plasma concentrations compared to an equivalent dose of bupivacaine, thus allows for a longer duration of effect without increasing plasma concentrations.(11) Several publications utilizing regular bupivacaine for injection into the cesarean incision, for incision infiltrations, and for TAP blocks. These studies have demonstrated its safety when used in the operating room and with lasting effect into the immediate postpartum period.(13,16,21–26) Its safety has also been demonstrated with lactation.(27) Liposomal bupivacaine has also been demonstrated to be safe when injected into the cesarean incision and when utilized for TAP block.(9,12,28,29)

For the purpose of this study, the control arm and intervention arm will receive the following medications via surgical TAP block:

Control Arm	Intervention Arm
30 mL bupivacaine HCl 0.25% 50 mL saline Total: 80 mL Inject 40 mL on each side	30 mL bupivacaine HCl 0.25% 30 mL saline 20 mL (266 mg) liposomal bupivacaine Total: 80 mL Inject 40 mL on each side

These injections will be performed once during this surgery itself. Because liposomal bupivacaine has a hazy appearance and is not clear due to the presence of liposomes, this study will be single blind as there is no equivalent appearing control.

6. Study Objectives and Endpoints

6.1 Objectives

The purpose of this study is to determine whether liposomal bupivacaine administered via surgical TAP block at the time of Cesarean delivery will reduce the total dose of opioids received. Our hypothesis is that liposomal bupivacaine will reduce the total dose of opioids received in the immediate 48 hours post-delivery.

Secondary outcomes will include

- patient self-reported pain scores.
- patient-reported incidence of side effects.
- development of objective complications such as dysrhythmias.

- Percentage of postpartum people who are "opioid free" at each timepoint (12, 24, 48, 72 hours, and during the hospitalization) with “Opioid free” defined as not receiving any opioid medication after surgery.

Percentage of postpartum people who are “Opioid spared” at each timepoint (12, 24, 48, 72 hours, and during the hospitalization) with "Opioid spared" defined a priori as taking ≤15 mg oral morphine equivalent dose at that timepoint after surgery

Other outcomes collected will include:

- length of stay
- time to first rescue analgesic medication
- total dose of opioids at 12, 24, 36, 72 hours and during the hospital stay
- use of supplemental oxygen during hospitalization
- breastfeeding rates, both exclusive and in combination with formula use
- amount of opioid prescribed at discharge and whether refills were requested or administered
- rates of chronic pain at six weeks postpartum
- six week Edinburgh Depression Screen scores
- % subjects who use 0 MME in each group for each time period
- % subjects who used 15 MME or less
- % subjects who report pain score of 7 or higher at each time point

Neonatal outcomes such as fetal weight, five-minute Apgar scores and development of adverse outcomes such as NICU admission will also be collected because NICU admission can impact maternal opioid use.

6.1.1 Primary Objective:

- To determine whether liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery will reduce the total dose of opioids received in the first 48 hours after surgery.
- *Hypothesis:* Our hypothesis is that liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery will reduce the total dose of opioids received in the first 48 hours after surgery.
- Developmental SubAim: If liposomal bupivacaine administered via surgical TAP block does reduce the total dose of opioids received, to determine the degree of the reduction in order to allow for an adequately powered randomized-controlled trial.

6.1.2 Secondary Objective:

- To determine whether liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery will reduce patient-reported pain scores and opioid-related side effects, including respiratory compromise.
- *Hypothesis:* Our hypothesis is that liposomal bupivacaine administered via surgical TAP block at the time of cesarean will reduce patient-reported pain scores and opioid related side effects.

6.2 Endpoints

6.2.1 Primary Endpoint:

- The primary endpoint or primary objective is to reduce the total dose of opioids received in the first 48 hours post-op after cesarean delivery. All opioid doses will be converted into oral morphine equivalents for standardization purposes.

6.2.2 Secondary Endpoint(s):

- Median postoperative pain score for the first 24 hours post-operatively measured by the Numeric Rating Scale (NRS) which rates pain on a 0-10 scale, collected routinely on the postoperatively floor by nurses as per their standardized routine. UnityPoint Meriter’s Assessment of the Postpartum Patient

Standard of Care Document #29 (UnityPoint-Health Meriter Nursing Policy Document) states that pain assessment documentation should be done every shift and before and after giving pain medication to ensure that patients are getting adequate relief. Thus, pain will be assessed approximately every 4-6 hours. This outcome, therefore, will be recorded from the EMR.

- Maximum and minimum pain scores every 6 hours throughout the whole hospital stay as measured by the NRS above extracted manually from the electronic health record.
- Frequency of patient-reported opioid-related side effects, such as pruritis, constipation, nausea, and mental clouding.
- Incidence of complications of bupivacaine, such as local burning, nausea, dizziness, drowsiness, serious skin reactions such as blistering, confusion, blurred vision, ringing in the ears, arrhythmias, methemoglobinemia, and allergies and hypersensitivities.
- Post-operative anti-emetic use and number of recorded episodes of emesis.
- Return of bowel function (measured in hours from completion of surgery to passage of flatus)
- Length of hospital stay, measured in hours from admission to time of discharge order placement
- Time to first rescue analgesic medication, measured in minutes from arrival in the post-anesthesia care unit (PACU) until the first as needed opioid dose is administered
- Total dose of opioids used in the first 48 hours post-operatively. All opioid doses will be converted into oral morphine equivalents.
- Total dose of opioids during the whole hospitalization. All opioid doses will be converted into oral morphine equivalents.
- Postoperative complications, such as urinary tract infections, thromboembolic events, pneumonia, postpartum blood transfusions, falls, myocardial infarctions.
- Amount of opioid prescribed at discharge, measured as both the number of pills and the dose of opioids.
- Routine obstetric/ maternal outcomes will be collected.
- Neonatal outcomes, including Apgar scores, NICU admission and reason, birthweight, gestational age at delivery, and other routine neonatal outcomes.
- A secondary analysis will also be performed analyzing the effect of the liposomal bupivacaine administered via surgical TAP block on opioid dose and pain score stratified by BMI.
- We will also analyze the overall cost effectiveness of liposomal bupivacaine administered via surgical TAP block in terms of overall hospital costs, if it is proved to reduce pain and opioid dose.

6.2.3 Correlative objectives:

- Breastfeeding rates, both exclusive and breastfeeding with supplementation at the time of discharge.
- Readmission rate.
- Whether opioid refills were requested, assessed at 2 and 6 weeks postpartum.
- Number of remaining opioid pills (of those prescribed), assessed at 2 and 6 weeks postpartum.
- Rates of ongoing pain at 2 and 6 weeks postpartum. Edinburgh Depression Screen (EDS) Scores assessed at 2 and 6 weeks postpartum.
- Satisfaction scores at 2 and 6 weeks postpartum as measured by two pain satisfaction questions taken from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS survey)

7. Study Design

7.1 General Design

- This study will be a single-center, single blind, randomized controlled trial. The study will be conducted at UnityPoint-Health Meriter Hospital under investigators from the University of Wisconsin-Madison. Obstetric patients undergoing Cesarean delivery at UnityPoint-Health Meriter will be eligible.

- The rationale for this study being a pilot randomized controlled trial is that the liposomal bupivacaine has never been administered via surgical TAP block at the time of cesarean, therefore an effect size cannot be estimated from the literature.
- The rationale for this study being single blind is that a control with a similar appearance to the liposomal bupivacaine is not available from the drug manufacturer or another pharmaceutical company. Because the injections will not be available, the providers will be able to identify whether the control or intervention is being utilized.
- The injection will occur one time and will be administered via surgical TAP block at the time of cesarean delivery.
- The study groups will consist of two arms:
    - One arm will receive the intervention injection which comprises 30 mL of bupivacaine HCl 0.25%, 30 mL of saline, and 20 mL of liposomal bupivacaine (266 mL) for a total of 80 mL with 40 mL injected on each side.
    - The other arm will receive the control injection which comprises 30 mL of bupivacaine HCl 0.25%, and 50 mL of saline for a total of 80 mL with 40 mL injected on each side.

7.2 End of Study Definition

A subject is considered to have completed the study when she has completed all phases of the study. Primary endpoints occur at 48 hours after cesarean completion. Additional outcomes will be collected at two and six weeks post-Cesarean.

8. Subject Selection

8.1 Target Study Sample Size

- The target sample size for a pilot RCT was determined to be 50 with 25 subjects per arm. However, in order to account for up to a 20% dropout, we seek to randomize 60 subjects with 30 per arm.
- We anticipate that maximum number of subjects screened to reach this sample size will be 3000. This approximates the number of women who undergo Cesarean delivery at UnityPoint-Health, Meriter in a 24 month period. The most likely scenario is that less subjects will need to be screened because many unplanned or urgent cesarean births would not be eligible.
- The anticipated goal is 60 subjects randomized.
- Subjects will be counted once they are randomized, not at the time of consent. This is because many subjects who are planning for a cesarean delivery do not ultimately have their surgery performed on the day that it is scheduled due to either going into labor prior to the scheduled date or having another indication for delivery prior to the scheduled date. When this occurs, randomization may or may not occur depending upon staff availability around the time of delivery.
- Subjects will be enrolled and randomized while pregnant but when delivery via cesarean is imminent. The intervention will occur immediately after delivery while the surgery is ongoing. This intervention, since it will occur postpartum, will not impact the fetus because at the time of intervention the pregnancy will have been completed.

8.2 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Maternal age greater than or equal to 18
- Singleton or multifetal pregnancy
- Able to receive neuraxial analgesia
- Planned/ scheduled Cesarean delivery OR non-urgent Cesarean delivery with adequate time to consider and consent to the study
- Able to provide consent in English

8.3 Exclusion Criteria

An individual who meets any of the following criteria is not eligible to participate in this study and is excluded:

- Known hypersensitivity to bupivacaine or liposomal bupivacaine (defined as a history of a reaction or allergy to bupivacaine (injectable, intravenous, or transdermal) reported by patient or documented in the medical record) or patient report
- Plan by the obstetrical provider to inject bupivacaine or other local anesthetic into the cesarean incision due to potential differences in pain levels.
- Contraindication to regional analgesia
- Positive urine drug screen at admission to the hospital, if ordered for clinical purposes.
- Current opioid use or opioid use disorder per patient report or documented in the medical record or the ePDMP (reviewed by PI 1-14 days prior to surgery)
- Chronic opioid use or opioid use disorder, either patient reported or documented in the medical record or the ePDMP (reviewed by PI 1-14 days prior to surgery), defined as opioid use on most days for >3 months
- Planned Cesarean hysterectomy (excluded due to anticipated blood loss and alternative pain control measures, possible prolonged intubation)
- Planned vertical midline incision
- Presence of renal dysfunction precluding the use of NSAIDs
- Ischemic heart disease, congestive heart failure, or cardiomyopathy of pregnancy
- Coagulopathy
- Planned discharge from the hospital less than 48 hours postpartum
- Unable to receive post-operative scheduled acetaminophen for any reason, such as allergy to acetaminophen or elevated liver function tests precluding acetaminophen use
- Unable to receive post-operative scheduled NSAIDs for any reason, such as allergy to ketorolac or ibuprofen, or renal dysfunction precluding NSAID use.
- Due to an adverse event where a patient experienced local anesthetic systemic toxicity, the anesthesiology group at UPH-Meriter proposes additional exclusion criteria for this study protocol. These patients are still able to receive local anesthetics and bupivacaine and liposomal bupivacaine, but because they are the team that would manage a toxicity reaction, they would feel more comfortable placing these TAP blocks themselves rather than having them be in this study protocol.
  - Seizure disorder: Specifically, poorly controlled seizure disorder defined as having had a seizure within the last three years despite antiepileptic use or poorly managed seizure disorder due to medication non-compliance.
  - Cardiac disease or arrhythmia: Defined as ischemic heart disease, peripartum cardiomyopathy, heart failure (with reduced or preserved ejection fraction, compensated or decompensated). Patients with a remote history of non-cyanotic pediatric cardiac surgery (like a VSD closure or PDA ligation as a child) do not need to be excluded. History of adult cardiac surgery without ongoing problems or treatments other than chronic anticoagulation (mitral valve repair for MVP or aortic valve replacement for bicuspid aortic valve for example) would not need to be excluded. History of repaired congenital cyanotic heart disease should be considered for exclusion, ultimately up to the anesthesiologist that day. A patient with a history of arrhythmias not requiring medication or ablation would NOT need to be excluded and could be included in the study. History of ablation or active anti-arrhythmic medication should be considered for exclusion.
  - Hypoxia: Defined as requiring supplemental oxygen during the day.
  - Acidosis. This will be uncommon in our population, but if someone has active diabetic ketoacidosis will exclude.

8.4 Recruitment

- Primary obstetric providers will be made aware of this study using IRB-approved study posters, fliers, and brochures.
- Providers will provide the woman with information and a consent form and have the patient sign a "Permission to Contact" form, performing a preoperative examination on a woman who meets criteria for enrollment in the study
- The study coordinator or study staff will call the patient and read a prepared script about the study.
- If the patient is interested, the study coordinator or study staff will review the informed consent document during the telephone call.
- At a following clinical appointment or on the day of surgery, the research coordinator or study staff will review again the informed consent document and the patient will sign it if they would like to participate.
- Preliminarily eligible subjects will be invited to the Meriter Center for Perinatal Care or their assigned room in triage or the antepartum or intrapartum ward for informed consent and formal screening.

8.5 Retention Strategies

- Subjects will not be compensated for participating in this project.
- After enrollment, there will be an in-person randomization and the surgical TAP block will be administered at the time of their cesarean delivery.
- Two week postpartum follow-up will comprise questions about breastfeeding, number of opioid pills remaining (of those prescribed) and questions about satisfaction with care.
- Six week postpartum follow-up will comprise questions about breastfeeding, number of pills left and questions about satisfaction with care.
- These questions will be sent via email message link to a secure survey for the participant to complete.

8.6 Early Termination and Withdrawal

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- If study procedures are discontinued due to AE
  - After the intrapartum period, if the subject develops serious skin reaction, or hypersensitivity/ allergy.
- Protocol violation
- Study terminated
  - If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation]

Subjects who sign the informed consent form and are randomized but do not receive the study intervention will be replaced. Subjects who sign the informed consent form, are randomized and receive the study intervention, then subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

9. Study Intervention

9.1 Study Intervention Description

The study intervention will consist administering the study injection (either the intervention injection which comprises 30 mL of bupivacaine HCl 0.25%, 30 mL of saline, and 20 mL of liposomal bupivacaine (266 mL) for a total of 80 mL with 40 mL injected on each side or the control injection which comprises 30 mL of bupivacaine HCl 0.25%, and 50 mL of saline for a total of 80 mL with 40 mL

injected on each side) at the time of cesarean delivery. This injection will occur only once and will occur at the time of cesarean.

9.2 Source

The intervention drug and control drug will be purchased by and supplied to the investigator via the Pharmaceutical Research Center (PRC) pharmacy research center at the University of Wisconsin-Madison. Hospitals and Clinics (UWHC). The PI has corresponded with the PRC regarding obtaining these medications and has received confirmation that they can be obtained and the cost.

9.3 Packaging and Labeling

- The intervention drug will be supplied by Pacira Biosciences, Inc. (NDC 65250-266-29).(30)
- It is labeled as “Exparel (Bupivacaine liposome injectable suspension).
- The instructions indicate that vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F).
- The intervention drug may be held at a controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 30 days in sealed, intact (unopened) vials.
- Do not re-refrigerate vials.
- Do not freeze or expose liposomal bupivacaine to high temperatures (greater than 40°C or 104°F) for an extended period.
- Do not administer liposomal bupivacaine if it is suspected of having been frozen or exposed to high temperatures.
- Do not use the vial if the stopper is bulging.
- Handling
    - Invert vials of liposomal bupivacaine to re-suspend the particles immediately prior to withdrawal from the vial.
    - Multiple inversions may be necessary to re-suspend the particles if the contents of the vial have settled.
    - Visually inspect vials for particulate matter and discoloration before use.
    - Do not filter.
    - Do not heat before use.
    - Do not autoclave.
    - Following withdrawal from the vial, store liposomal bupivacaine at controlled room temperature of 20°C to 25°C (68°F to 77°F) for up to 4 hours prior to administration.
    - Discard any unused portion in an appropriate manner.

The control drug will be handled as per the usual protocol as it is already in semi-routine use for injections into other sites at the time of cesarean.

9.4 Preparation

Both the intervention and the control injections will be prepared by mixing with regular bupivacaine HCl 0.25% and saline as follows:

Control Arm	Intervention Arm
30 mL bupivacaine HCl 0.25% 50 mL saline Total: 80 mL Inject 40 mL on each side	30 mL bupivacaine HCl 0.25% 30 mL saline 20 mL (266 mg) liposomal bupivacaine Total: 80 mL Inject 40 mL on each side

These medications will be mixed in the operating room by study staff or nursing staff who have been educated on the handling of liposomal bupivacaine.

9.5 Storage and Stability

UW PRC will create study drug kits containing either the intervention or the control. These will be labeled sequentially with ascending sequential randomization numbers and will contain the medications for the control arm (bupivacaine and saline) or the intervention arm (bupivacaine, saline, and liposomal bupivacaine). Ancillary supplies (syringes, needles) will be in a separate package. Kits stored at room temperature will need to be utilized within 30 days. Kits stored in a refrigerator will not need to be used within 30 days.

Kits stored in a refrigerator will be located within a locked refrigerator in a locked room. Kits stored at room temperature will be within a locked cabinet in a locked room and will need to be used within 30 days.

After a participant is consented and randomized, we will pull the next unused kit for use with that participant. The participants study ID information will be recorded on a log created by the UW pharmacy to ensure that all regulatory information is documented.

The kit will then be brought to the operating room to use at the end of the cesarean surgery.

The physician performing the surgery will open the contents of the “kit” as described above while handling all drugs appropriately. The products will be mixed as above, and administration of the “study drug” will be documented in the operative note and the medication administration record within the electronic health record.

Measures will be taken to ensure limited access as well as measures to prevent accident damage or destruction.

If “kits” are not able to be used, we will plan to store the components separately at the temperature at which they are most stable and will assemble the kits as needed based upon the randomization sequence with the assembling providers blinded until the allocation envelope is opened.

9.6 Accountability

Quality review activities related to the receipt, storage, dispensing, tracking, and destruction are performed to ensure proper accountability of the investigational product. The MOP describes the processes for the ordering, maintenance, and dispensing of the study drug. Investigator(s) and study team members ensure

that informed consent is obtained before the investigational product is administered to study subjects, and the investigational product is only administered to those subjects eligible for and enrolled in the clinical trial.

9.7 Dosing and Administration

The liposomal bupivacaine will be administered via surgical TAP block after delivery of the fetus and closure of the hysterotomy but prior to closure of the fascia. Only providers trained on performing this procedure may perform it for the study protocol. All patients in both arms will be administered additional analgesia in accordance with post-cesarean pain control as per hospital guidelines. The expected “Study Drug Schedule” is included in this documentation.

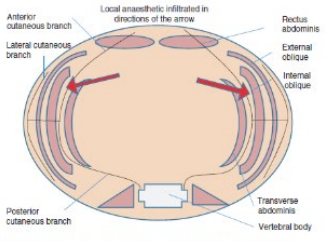


Figure 1. Schematic representation of the innervations of anterior abdominal wall.

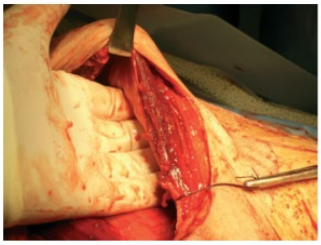


Figure 3. Surgeon locating the inferior epigastric vessels.

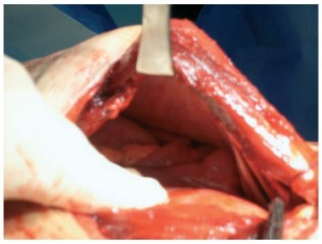


Figure 2. Rectus muscle is gently elevated using a retractor.

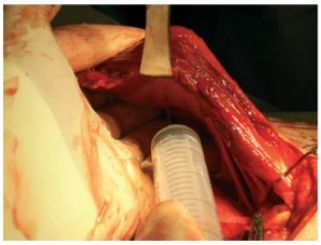


Figure 4. Safe access to transversus abdominis plane by inserting a blunt needle through parietal peritonium and transversus abdominis muscle

The administration will occur as follows[1,2]:

Having closed the uterus and established hemostasis at the incision, the rectus muscle is gently elevated superiorly using a retractor (figure) and the surgeon palpates its lateral border. This indirectly locates the inferior epigastric vessels which ascend between the rectus abdominis and posterior lamella of its sheath. The nerves that supply the anterior abdominal wall travel through the neurofascial plane between internal oblique and transversus abdominis muscles. Access to this plane can be achieved by inserting an 18-22 gauge blunted needle through the parietal peritoneum and with further advancement there is a loss of resistance and the correct plane has been entered. The presence of resistance to injection suggest the needle tip is too deep and is within the internal oblique muscle. Formation of a bleb in the peritoneum suggests the needle is too superficial and had not penetrated the transverse abdominis. If the needle is not in the correct plane, reposition it by retracting or advancing, respectively. After aspiration to ensure no vascular injury, 40 mL of bupivacaine is slowly introduced via two 20 mL injections into the area of interest. The surgical TAP block is then performed on the opposite side using an identical technique which may be performed by the other surgeon or by having the first surgeon move to the contralateral side of the table.
By directly visualizing the injection site, the surgeon ensures no inadvertent damage to the viscera.
Following surgical TAP block, the fascia, subcutaneous tissue, and skin are closed in the usual fashion per the usual surgical protocol.
Tip: a sponge may be inserted in the paracolic gutter to pack the bowel away if they impede access.

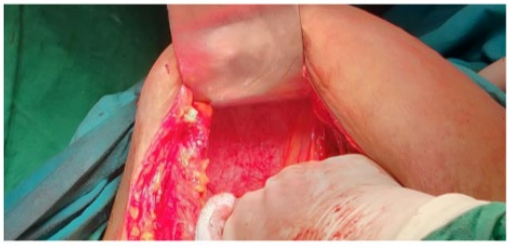


Fig. 1 Depicting the landmark for needle puncture

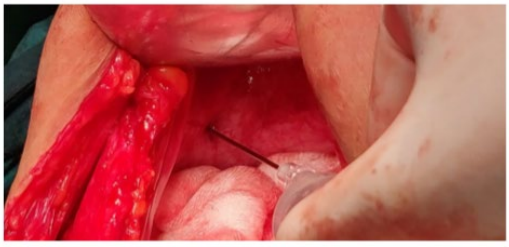
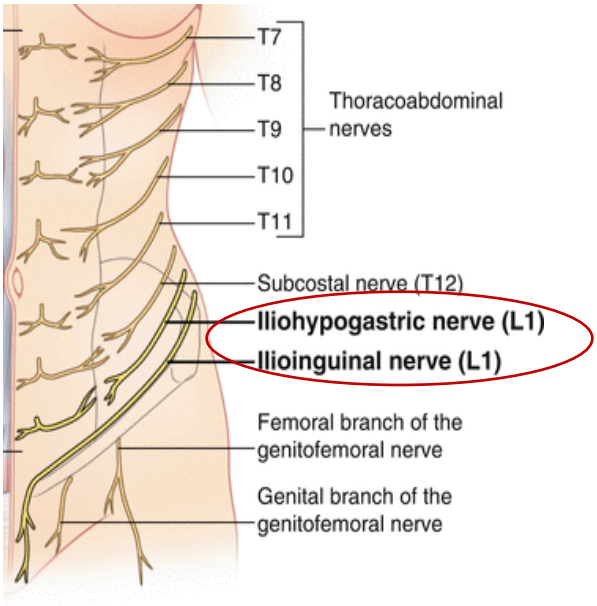
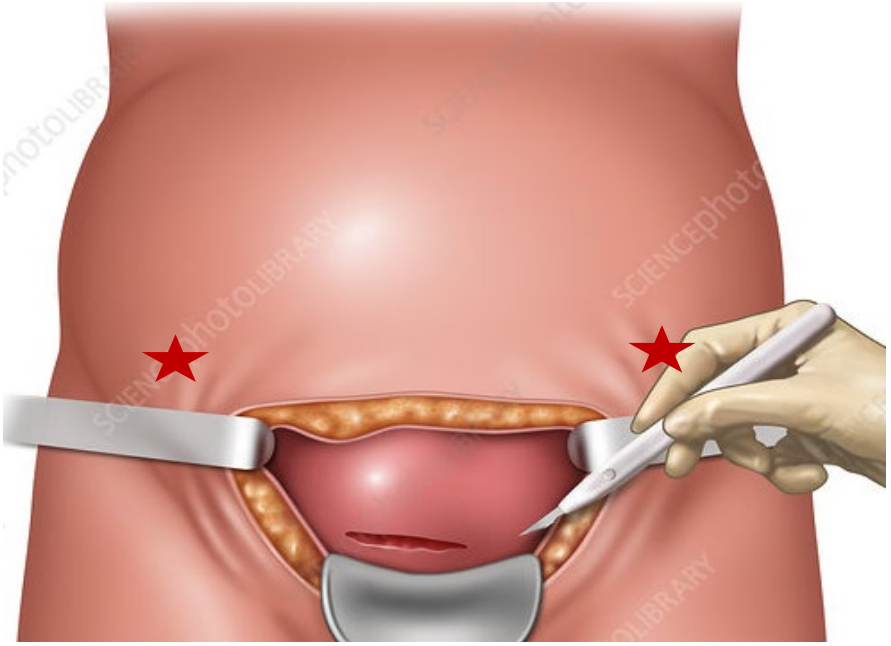


Fig. 2 Depicting the needle puncture

Dosing location:





9.7.1 Dose Schedule

	Enrolled	
	Randomization	
	Intervention arm	Control arm
Intraoperative	Standard regional analgesia	Standard regional analgesia
Prior to closing fascia	30 mL bupivacaine HCl 0.25% 30 mL saline 20 mL (266 mg) liposomal bupivacaine Total: 80 mL Inject 40 mL on each side	30 mL bupivacaine HCl 0.25% 50 mL saline Total: 80 mL Inject 40 mL on each side
At arrival to PACU	15 mg IV ketorolac + 975 mg PO acetaminophen	15 mg IV ketorolac + 975 mg PO acetaminophen
Anytime post-op	Morphine IR PO 7.5-15 mg Q 4 hours PRN for moderate to severe pain* *CAN increase to 15-30 mg Q4 hours PRN if pain is not controlled *CAN also use Hydromorphone IV 0.5-1 mg Q2 hours PRN for moderate to severe pain for breakthrough pain or if not yet tolerating PO OR any other opioid medications on formulary	Morphine IR PO 7.5-15 mg Q 4 hours PRN for moderate to severe pain* *CAN increase to 15-30 mg Q4 hours PRN if pain is not controlled *CAN also use Hydromorphone IV 0.5-1 mg Q2 hours PRN for moderate to severe pain for breakthrough pain or if not yet tolerating PO OR any other opioid medications on formulary
Every 6 hours postop	15 mg IV ketorolac (or 600 mg ibuprofen after 24 hours postop) + 975 mg PO acetaminophen + Resume postoperative pain regimen	15 mg IV ketorolac (or 600 mg ibuprofen after 24 hours postop) + 975 mg PO acetaminophen + Resume postoperative pain regimen

9.7.2 Dose Adjustments/Modifications/Delays

If a study participant experiences an allergic reaction to bupivacaine or does not tolerate it for any reason including, but not limited to, pain, irritation, desire to discontinue, the study team will be notified.

9.8 Randomization and Blinding

A randomization schedule will be created by the study statistician and will follow a block randomization with random block sizes of 4 or 6. This method will ensure balance in sample size per arm throughout the entire study. Ultimately, there will be 30 subjects per arm for a total of 60 subjects. The study ID numbers will be sequentially assigned to participants in the order that they are enrolled and consented. Randomization IDs will be sequentially assigned on the day of or the day before their surgery by the research coordinator or physician performing the procedure. The patient/ participant will be blinded to the subject's allocation. However, because the injections are not identical in appearance, the clinical team and research coordinators will not be blinded. Therefore, since the research coordinators are not

blinded, they may perform the randomization and will know the subject's allocation. Outcome measures are objectively measured and participants will be blinded to allocation.

9.9 Study Intervention Compliance

This section describes the strategy, responsibilities, and quality management activities in place to demonstrate that there is adequate monitoring of the clinical trial by the Principal Investigator (PI) to ensure:

- The trial is conducted according to the investigational plan, protocol and applicable laws, regulations, policies and guidance
- The rights, welfare, and safety of human subjects are protected
- Proper reporting of study data to the FDA and IRB
- The PI is providing adequate oversight of the clinical trial

The plan includes both internal quality and external, independent safety management processes used throughout the study, including but not limited to staff training, standardized procedures, methods for data collection, study and data monitoring, and routine team meetings to review the study progress and isolate any compliance issues and/or trends.

9.9.1 Study Team Training

Members of the study team are trained on the protocol and/or study procedures applicable to their roles and responsibilities. When the protocol and/or study procedures are updated, staff will be trained on the revisions prior to implementation, as applicable.

Per University of Wisconsin-Madison policy, all personnel engaging in human subjects research must complete Human Subjects Protection, and Health Insurance Portability and Accountability Act (HIPAA) training. In addition, those engaged in applicable clinical trials must also complete the Good Clinical Practice (GCP) training.]

Training is documented and maintained in the study files.

9.9.2 Investigator/Study Team Member Agreement

All members of the study team are informed of their responsibilities specific to their role(s) in this study, their obligation to follow the approved clinical research protocol, the applicable regulations, guidelines and institutional policies. Documentation of this agreement is maintained in the study files.

9.9.3 Financial Disclosure

Financial disclosure information is collected for all members of the study team that make a direct and significant contribution to the data. Financial disclosure documentation is maintained in the study files.

9.9.4 Routine Study Team Meetings

Routine study team meetings ensure on-going supervision and oversight of the study and study personnel involved in the conduct of the study will be held on a weekly and then bi-weekly basis: weekly in the weeks before and immediately after study initiation and bi-weekly once the team has determined that weekly meeting are no longer needed by any study personnel. In the meetings, the sponsor, sponsor-investigator, and/or the principal investigator (PI) (if not one in the same) and study team members discuss evaluations of study-related activities (as applicable): identification of deviations or noncompliance, review of adverse events, and overall study progress. Training on protocol, procedure and/or form updates may also be performed during routine meetings.

9.9.5 Standardized Procedures

9.9.5.1 Standard Operating Procedures (SOPs)
Study teams are trained on and must follow the Department of Obstetrics & Gynecology (Ob/Gyn) Clinical Research SOPs to ensure consistent performance of procedures by all team members and across protocols within the clinical research office. SOPs are periodically reviewed and updated (as necessary).

9.9.5.2 Manual of Procedures (MOP)
The MOP is a supplemental guide to the study protocol and complements Department SOPs to provide additional details on the conduct of the study. It is routinely updated to ensure consistent performance of study activities.

9.9.6 Additional Measures in place.
Refer to the following section(s) of the protocol for additional quality assurance measures that will be taken.
11. Data Collection, Handling and Record Keeping
12. Assessment of Safety
14. Regulatory, Ethical, and Study Oversight Considerations
14.1 Safety Oversight
14.2 Protocol Deviations

9.10 Concomitant Therapy
All patients in this study will be receiving the standard post-cesarean analgesia regimen as detailed above. Unless specifically listed in the exclusion criteria (above), other concomitant medications will be recorded on the CRF but will be permitted. Concomitant therapy might affect the outcome due to drug-drug interactions or altered metabolism.

9.11 FDA IND Compliance
The liposomal bupivacaine intervention used for the purposes of this study is for the indication of pain control, which is its listed indication. This medication has also been used for TAP blocks at cesarean. The subjects being studied are not considered a vulnerable population, posing no additional risks regarding the use of the study intervention. This study does not need to be conducted under an Investigational New Drug (IND) application with the FDA, rather is considered IND Exempt as it is being used in the context in which it was approved.

This study meets the IND Exemption criteria as defined by 21 CFR 312.2(b) Exemptions.
(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug; The results of this study will not be reported to the FDA to support a new indication or use, or change in labeling of the drug.

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product; The study intervention is lawfully marketed and is not intended to support a significant change in the advertising of the product.

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; The study intervention will be administered using the dosage and route of administration as well as the patient population (in need of pain relief) that is approved.

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth

in part 56 and with the requirements for informed consent set forth in part 50; and the investigation will be conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50.

(v) The investigation is conducted in compliance with the requirements of 312.7. The intervention used in the study will not presented as safe or effective for the purposes for which it is under investigation or otherwise promote the drug.

10. Study Visits and Procedures

10.1 Study Calendar

Event	Activity 1	Activity 2	Activity 3	Activity 4
Timing	Clinic, ultrasound unit, triage, via telephone, or labor and delivery prior to Cesarean delivery. May occur on same day as activity 2 or may occur prior.	At the time of Cesarean delivery	2 weeks postpartum	6 weeks postpartum
Location	See 10.2.1	OB triage, antepartum unit, or labor and delivery (L&D) room L&D OR (for Cesarean delivery)	Pt's home: Email message link to survey + (Emails x up to 4) Telephone reminder (If no prior response)	Pt's home: Email message link to survey + (Emails x up to 4) Telephone reminder (If no prior response)
Events	Consent	-Randomization (to occur day of or day before surgery) -Cesarean delivery (clinical event) -Liposomal bupivacaine administered via surgical TAP block	Survey completed	Survey completed

10.2 Screening and Enrollment

The Screening and Enrollment activities and procedures are described in detail below.

10.2.1 Prescreening

Potentially eligible subjects will be identified and approached at different time points during pregnancy and at various locations. Women may be approached or consented at any of the time periods below (to allow for many possible opportunities to have the study discussed, but once they indicate they are not interested they will not be re-approached.) For each scenario, the initial approach will be done by nurses, residents, providers or other clinical staff not on the study or study coordinators. Clinical staff will only approach the patients about

participation in a research study, but not include specifics about this study. These scenarios and mechanisms are described below:

General Recruitment and Enrollment Mechanism:

1. Providers:

Primary obstetric providers will be made aware of this study and IRB-approved study posters, fliers, and brochures will be made available to interested primary obstetric providers.

a. When providers perform a preoperative examination on a woman who meets criteria for enrollment in the study, they will provide the woman with information and a consent form and have the patient sign a "Permission to Contact" form.
b. Physicians or other clinical care team member can also obtain verbal permission from the potential subject to be approached by the coordinator.

2. Study Coordinators:

Inpatient Only: Coordinators work with nursing staff to identify a time when patient is not sleeping or involved in a medical procedure to approach the patient.

The study coordinator or study staff will then call the patient and read a prepared script about the study. If the patient is interested, the study coordinator or study staff will review the informed consent document during the telephone call. At a following clinical appointment or on the day of surgery, the research coordinator or study staff will review again the informed consent document and the patient will sign it if they would like to participate. Consent may also occur via a virtual visit.

Preliminarily eligible subjects will be invited to the Meriter Center for Perinatal Care or their assigned room in triage or the antepartum or intrapartum ward for informed consent and formal screening.

Randomization will occur the day before the planned surgery or the day of the planned surgery.

Inclusion of Patients who speak Spanish

The study will enroll subjects who speak and read either English or Spanish.

All documents, including the consent and HIPPA authorization form are translated into Spanish by a certified medical interpreter in the UW Hospital Interpreter Services Department.

An interpretation service, LanguageLine, will be used during the informed consent process, telephone conversations or other verbal interactions with subjects. Non-English-speaking patients who require a Spanish interpreter may only be consented if a language line representative is available.

**First Approach and Permission to Contact

The coordinator will use LanguageLine in all scenarios for first approach. The coordinator will call LanguageLine to go over the consent form or permission to contact with the patient.

If there is no interpreter present, permission to contact will be delayed. The patient needs to be able to understand and communicate with the coordinator. No communication will be done for research purposes until LanguageLine is available.

Every effort will be made to approach Spanish speaking subjects at the same locations/circumstances as non-Spanish speaking patients.

Fetal anatomic examination ultrasound: Meriter Center for Perinatal Care
Initial Approach: Patients undergoing a detailed fetal anatomic examination ultrasound (CPT code 76811) at the Meriter Center for Perinatal Care will be provided with an information about this study. This sonogram typically occurs at 18-22 weeks gestational age, which is approximately five months prior to delivery. (CPT code 67811 examinations occurring at other gestational ages will also be permitted.) However, this sonogram may occur at later gestational ages and information will be provided at this visit regardless of gestational age.

The initial approach will be done by nurses, residents, providers other clinical staff or study coordinators. Clinical staff will only approach the patients about participation in a research study, but not include specifics about this study. Physicians or other clinical care team member can also obtain verbal permission from the potential subject to be approached by the coordinator.

Follow-up and Informed Consent: Research coordinators or study staff will contact subjects by telephone who give permission to contact, and they will read a prepared script to the patients to describe the study. If the patient is interested, an informed consent document will be mailed to the patient to review. The research coordinator or study staff will re-connect with the patient when the patient presents for a third trimester growth sonogram or any other visit to Meriter or the day of surgery and they will review study eligibility criteria and whether a Cesarean delivery is planned. If a Cesarean delivery is planned, then the coordinator or study staff will have the patient sign an informed consent document at that time. Consent may also occur via a virtual visit. Then, 0-3 days prior to the Cesarean delivery, the research coordinator or study staff will re-connect with the patient to confirm eligibility and desire to be in the study.

Third Trimester: Anesthesia preoperative consultation
Initial Approach: At Meriter Center for Perinatal Care, some patients complete an anesthesia consultation during the antepartum period. This is a clinical protocol and is not related to this study. Of note, these patients would not constitute a separate cohort, but the existence of this clinic does allow providers another opportunity to identify eligible patients.

The initial approach will be done by nurses, residents, providers other clinical staff or study coordinators. Clinical staff will only approach the patients about participation in a research study, but not include specifics about this study. Physicians or other clinical care team member can also obtain verbal permission from the potential subject to be approached by the coordinator.

Follow-up and Informed Consent: If such patients are scheduled for a Cesarean and have an anesthesia appointment, the research coordinator or study staff will approach them for enrollment at their anesthesia preoperative appointment. This appointment typically occurs around 32 weeks of gestation; any gestational age will technically be eligible for approach and consent. The women, therefore, will sign consent at that time and she will be told to expect a telephone call the day before the surgery to confirm eligibility and intent to participate in the surgery. Consent may also occur via a virtual visit.

28-38 weeks gestation ultrasound: Meriter Center for Perinatal Care
Initial Approach: Patients undergoing a growth ultrasound examination (goal 28-38 weeks, but any gestational age acceptable) at the Meriter Center for Perinatal Care with a possible plan for scheduled cesarean will be provided with an information sheet about this study and a permission to contact form. This sonogram typically occurs at 36 weeks gestational age, which is approximately 3-4 weeks prior to delivery, but growth ultrasounds occurring at any time will be permitted.

The initial approach will be done by nurses, residents, providers other clinical staff or study coordinators. Clinical staff will only approach the patients about participation in a research study, but not include specifics about this study. Physicians or other clinical care team member can also obtain verbal permission from the potential subject to be approached by the coordinator.

Follow-up and Informed Consent: Research coordinators or study staff will contact subjects by telephone who give permission to contact, and they will read a prepared script to the patients to describe the study. If the patient is interested, an informed consent document will be mailed to the patient to read and review. The research coordinator or study staff will also attempt to directly connect with the patient around 36 weeks when the patient presents for their growth sonogram, and they will review study eligibility criteria and whether a Cesarean delivery is planned. If a Cesarean delivery is planned, then the coordinator or study staff will have the patient sign an informed consent document at that time. Consent may also occur via a virtual visit. Then, 1-3 days prior to the Cesarean delivery, the research coordinator or study staff will re-connect with the patient to confirm eligibility and desire to be in the study.

Antepartum admissions with plan to remain inpatient until delivery via Cesarean
Initial Approach: Occasionally women are admitted during their pregnancy and need to stay inpatient until delivery. Examples of such cases include women with preterm premature rupture of the fetal membranes.

The initial approach will be done by nurses, residents, providers other clinical staff or study coordinators. Clinical staff will only approach the patients about participation in a research study, but not include specifics about this study. Physicians or other clinical care team member can also obtain verbal permission from the potential subject to be approached by the coordinator.

Follow-up and Informed Consent: The research coordinator or study staff will describe the study, give a copy of the informed consent document, and allow the patient to consider participation in this study. If the woman would like to participate, informed consent will be obtained, the form will be signed. Consent may also occur via a virtual visit.

Triage, Labor & Delivery and Main Operating Room Pre-Operative Area:
Initial Approach: The provider or research coordinator will also review the labor and delivery and main operating room schedule for Cesarean deliveries among women who meet inclusion criteria.

The initial approach will be done by nurses, residents, providers other clinical staff or study coordinators. Clinical staff will only approach the patients about participation in a research study, but not include specifics about this study. Physicians or other clinical care team member can also obtain verbal permission from the potential subject to be approached by the coordinator.

Follow-up and Informed Consent: Research coordinators or approved clinical providers will approach subjects, the study will be described to subjects, and informed consent will be obtained. Consent may also occur via a virtual visit. Randomization will occur that same day prior to the cesarean. Due to the busy nature of labor and delivery, this option may be limited to women who remain on labor and delivery for an adequate period of time to allow consideration of the study.

10.2.2 Informed Consent

The informed consent process will be conducted following all federal and institutional regulations relating to informed consent. Informed consent will be obtained prior to conducting any study related activities.
At the baseline study enrollment, the participant's eligibility will be assessed and the enrollment case report form will be completed. No physical examination will be performed. The estimated length of the interaction is 10-30 minutes to allow adequate time to review medical history and sign informed consent document.
The informed consent process may occur in person or via telephone or video visit (remote consent) depending upon relevant infectious-disease related clinical and research restrictions in place.
The informed consent process will be performed as follows:

1. The research coordinator or study staff will review the informed consent form and discuss the study in detail with the potential research subject.

2. The research coordinator or study staff will explain the study, its risks and benefits, and what would be required of the research subject.
3. The research subject will be given the opportunity to take the informed consent form home so that he or she may discuss it with family members, friends, clergy or others when possible.
4. The subject will have the opportunity to ask questions and have all questions answered by the research coordinator and/or PI.
5. The informed consent document must be signed and dated by the research subject.
6. The research coordinator or study staff will review the informed consent document to ensure that all fields that require a response are complete (i.e. checkbox marked yes or no, etc.) as applicable.
7. The research subject will be given a copy of the signed and dated informed consent form. The original signed informed consent form is kept in the locked OB/GYN research office in a locked file cabinet.

An information sheet about the TAP block is typically used by the surgeon as an illustration tool to describe the procedure to the patient. This might be used prior to consent when describing the study or after consent to clarify further questions or as part of the consent process if the surgeon is obtaining the consent.

Example of patient counseling about the drug and study intervention:

Patient counseling:
We would like to offer you a surgical transverse abdominis plane block with bupivacaine at the time of your cesarean. This is sometimes called a “TAP” block for short. This is a nerve block with a local anesthetic which should help reduce your pain. Historically, this block was placed by an anesthesiologist using an ultrasound to ensure the needle is placed in the correct place. However, we as surgeons are able to identify this correct location while we are doing the cesarean before we close your abdomen. This eliminates the main risk of the TAP block which is that the needle can accidentally puncture into the intestines or liver. Specific risks to all TAP blocks include bruising or hematoma formation, pain at the injection site, or inadvertent blockade of additional nerves. Risks of local anesthesia include cardiac risks, particularly if injected intravascularly. Other risks include neurotoxicity including seizures, blurred vision, ringing in the ears, and also allergic reaction. These are overall rare, and we take precautions to avoid intravascular injection by aspirating or pulling back on the syringe to ensure we aren’t in a blood vessel before we inject the anesthetic.

10.2.3 Baseline
At the baseline study enrollment, the participant’s eligibility will be assessed, and the enrollment case report form will be completed. No physical examination will be performed. The estimated length of the interaction is 10-30 minutes to allow adequate time to review medical history and sign informed consent document.

10.2.4 Subject Enrollment
For this study, due to the number of potential time points to obtain consent, and the large potential for dropout between consent and randomization, enrollment will be defined as the time of randomization. This accounts for women who may potentially present for delivery prior to their scheduled Cesarean date or who may no longer require a Cesarean delivery (example: breech presentation at 36 weeks which verts to cephalic prior to the scheduled Cesarean).

Procedures
- Informed Consent will be obtained and verified at any of the interactions listed above and by the latest on the day of the scheduled surgery

- Randomization will be performed by the research coordinator or approved clinical providers
- Delivery will occur via Cesarean delivery
- Following delivery of the baby and closure of the hysterotomy but before closing the fascia, the surgical TAP block will be administered utilizing liposomal bupivacaine as described above.

Postpartum

- All patients receive either Intervention Injection (liposomal bupivacaine plus bupivacaine HCl and saline) or Control Injection (bupivacaine HCl and saline) at the time of cesarean in addition to scheduled ketorolac and scheduled acetaminophen with additional opioids available PRN (See Table above)
- Pain will be assessed via the Numeric Rating Scale (NRS), which rates pain on a 0-10 scale, by the nursing team. Per unit protocol, this occurs every 4-6 hours.
- Outcomes data are collected by research coordinators

10.2.5 Screen Failure and Re-enrollment

Individuals who do not meet the criteria for participation in this trial (screen failure) due to no longer requiring a Cesarean delivery but then later have an obstetric situation change and then do require a Cesarean delivery will remain eligible. One example of this happening is a patient who has a breech baby who then has an external cephalic version and the baby is no longer breech. Some such patients will have a baby who then spontaneously verts to breech again and may ultimately require a Cesarean delivery. Therefore, individuals who meet criteria for participation will not be removed from the study until they have delivered (vaginally) at which point they will no longer be eligible for participation.

10.3 On-Study/Follow-up Activities

After subjects have been enrolled, the On-Study/Follow-up activities and the procedures are performed.

Randomization: the day before or day of the Cesarean delivery
The estimated time for randomization is about 10 minutes of research coordinator or approved clinical provider time. The enrollee will then have their Cesarean delivery (clinical) and have the liposomal bupivacaine administered via surgical TAP block.

Only the physicians listed on this application (or physicians in training that these physicians are directly supervising) will perform the study injections. Physicians in training includes residents and fellows.

A transversus abdominis plane block is not within standard training for OB/MFMs. However, it less complicated than many other procedures that we perform, and the technique can easily be learned. The physicians listed in this protocol have learned this procedure and have ensured proficiency by performing this procedure clinically with regular bupivacaine between October 2020 and February of 2021.

The Cesarean delivery will be performed by the clinical team as per the routine clinical protocol except that between closure of the hysterotomy and closure of the fascia the surgical transversus abdominis plane block will be placed. This procedure will only be performed by providers trained on the protocol. This procedure will occur in the operating room. The estimated time required to place the surgical TAP block is 2.4 minutes.(14) The research coordinator will then collect information on the total dose of opioids utilized and other outcomes. Study participation will be recorded in the EMR under Care Coordination Plan or Problem List.

Post cesarean follow-up surveys
Surveys will be emailed at 2 and 6 weeks postpartum, (each sent once if responded to, up to 4 times total sent every other day if no response) followed by a telephone call or text if there was no response to the emails. Patients who speak Spanish will only receive a phone call and not a text. The surveys can be

completed by the patient in the privacy of their own home on either a smart phone or computer. These study activities will be completed by the enrollee and if they fail to complete the survey after emails, they will be called. Data that will be collected will include the number of opioid pills the patient has remaining (of those prescribed) and patient satisfaction scores. Failure to complete these surveys will not be considered a protocol violation. Women who respond in the affirmative that they have poor mental/emotional health, are feeling depressed or other questions that relate to mental health or opioid addition, will be referred to the proper mental health or addiction counselor or provider.

As of this date, we do not have the means to provide non electronic survey copies as the subjects will be at home when they complete the surveys. In a future amendment, we will determine the best method for subjects without electronic means.

LanguageLine has the ability to do a conference call with the subject and coordinator. We will not be able to use text messages for patients who do not speak English. In a future amendment, we will determine the best method to communicate via text to subjects who do not speak English.

10.4 Unscheduled Visits

Unscheduled visits may occur if subjects would like to review the project or review their consent at any time. They may also be seen postpartum for any concerns that they think may be related to the study drug. (example: SAEs). However, unscheduled visits are not being specifically built into this study protocol.

10.5 Early Termination and Withdrawal

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Such reasons may include (but will not be limited to):

- Subject wishes to stop study involvement or withdraw for any reason.
- Subject has a complication from the Cesarean delivery and wishes to withdraw

The investigator also has the right to withdraw patients from the study for any of the following reasons:

- If study procedures are discontinued due to AE although their data would be retained for intention to treat analyses
- Protocol violation
- Study terminated
- If subject has a delayed complication from the cesarean delivery requiring re-operation although their data would be retained for intention to treat analyses

All data collected on subjects prior to their withdrawal or discontinuation will be retained. If a subject is withdrawn or discontinues study participation prior to their caesarean, the subject will be discontinued and replaced. If the subject is withdrawn or discontinues study participation after their caesarean, the subject will be followed with intent to treat and will not be replaced. The reason for subject withdrawal or discontinuation will be documented in the study records.

If a subject has signed informed consent but does not wish to undergo randomization, this will not count as a study discontinuation since they were not formally counted as “enrolled”.

Participants will not be informed of study results, but the results will be available to participants. These results would not be expected to be available until 2023 at the earliest. The treatment assignments will also not be disclosed to the subjects at the time of the study but will be available if they would like to know after the six-week follow-up is complete. If subjects would like to know their treatment allocation, they may call research coordinators for unblinding after the 6 week follow-up is complete.

11. Data Collection, Handling and Record Keeping

11.1 Data Collection

- Standardized data collection forms (e.g., source documents, case report forms, standardized assessment forms, etc.) are used to ensure data collected are consistent and compliant with the protocol and IRB application.
- Data collection is the responsibility of study team members under the supervision of the principal investigator. The principal investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the recorded and reported data.
- All data collection forms must be completed in a legible manner; any missing data will be explained. Data entry errors will be corrected with a single line through the incorrect entry and the correct data is entered above/near the correction. All changes will be initialed and dated.
- Data collection forms are maintained in the subject files and retained as described in the Record Retention section.

11.1.2 Data Collection Forms

Study team members use standardized data collection forms (e.g., case report forms, source documents, etc.) to ensure data collected are consistent and compliant with the protocol and IRB application. Forms are updated per protocol amendments (as applicable). Data will be handled in accordance with applicable regulations, GCP guidelines, as well as institutional policies.

11.1.3 Study Visit Checklists

Members of the study team use study visit checklists or worksheets, developed in conjunction with the sponsor-investigator and PI (if not one in the same), to ensure that all study required procedures and processes are conducted before, during and after the subject has been enrolled. These checklists are completed and reviewed by the members of the study team that interact with subjects and/or perform study procedures to ensure adherence to the protocol.

11.1.4 Source Documentation

The source document is defined as the first place the data are recorded. As per present, all source documents with patient data (i.e., “clinical metadata”) will be stored as paper records and considered the study source documents. All source documents will be maintained as hard copies and thereafter converted to electronic copies and secured in a manner accordant with the IRB protocol.

11.2 Record Retention

Records and documents pertaining to the conduct of this study, including CRFs, source documents, consent forms, and laboratory test results, must be retained by the investigator for a minimum of 7 years after study completion. Electronic data including clinical information data will be transferred to appropriate database(s). No study records shall be destroyed without prior authorization from the study PI (Antony) and/or the funding agencies, if applicable.

11.3 Handling of Data to Ensure Confidentiality

In order to ensure confidentiality of data the following procedures will be followed:

- Label the source documents with code numbers.
- Enter data from the source documents in a controlled-access database on the Internet or site proximal server.
- Store all source documents and consent forms in a locked file cabinet(s). Only members of the study team will have access to this file cabinet.

11.4 Data collection forms

11.4 Data Management Software System(s)

Clinical data (including AEs, concomitant medications, and solicited events data) and clinical laboratory data will abstracted from the patient's electronic medical record (EMR) and entered into the Research Electronic Data Capture (REDCap) data management software system(s) to ensure consistent data entry and data quality. Clinical data will be entered directly from the source.

REDCap is a largely self-service, secure, web-based application for building and managing data collection forms. REDCap provides data management functionality by allowing the development of instrument and surveys to support data capture for research studies

11.5 Data Confidentiality

11.5.1 Confidentiality of Subject Records

In order to ensure confidentiality of data the following procedures will be followed:

- Label the source documents with code numbers.
- Enter data from the source documents in a controlled-access database on the Internet or site proximal server.
- Store all source documents and consent forms in a locked file cabinet(s). Only members of the study team will have access to this file cabinet.

All the staff participating in this project have undergone human subjects protection, Good Clinical Practice (GCP), and HIPAA training.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). All subjects will sign an informed consent document and HIPAA authorization that includes specific privacy and confidentiality rights. Study data will be maintained per federal, state, and institutional data policies.

The Investigator(s) will ensure that the identities of subjects are protected by using coded subject information. The log of subject identifying information that links subjects to their study-specific identification number will be maintained by the Investigator. The log and all study records will be maintained in locked rooms and access will be limited to essential study personnel. Electronic study records/files will be stored on REDCap and on a department server and accessed via networked computers that are password-protected with access provided only to authorized study personnel.

Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research subjects: the study monitor, representatives of the IRB, DSMB/DMC, and DCC staff. The clinical study site will permit access to such records.

Study staff may use e-mail to communicate with research subjects, if the subject has agreed to using email in the Informed Consent form. Prior to any email exchanges, the study staff member will review the Use of Email for Research Purposes Guidance. The information contained in emails will be limited to study activity 3 and 4 which occur at 2 and 6 weeks postpartum. All emails to subjects will be sent from UW/wisc.edu accounts; personal, home or Gmail email accounts will not be used.

11.6 Records Retention

It is the investigator's responsibility to retain study essential documents for a minimum of period of 7 years following completion of the study per UW-Madison institutional policy, or at least 2 years after the last

approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever comes last.

12. Assessment of Safety

12.1 Risk/Benefit Assessment

12.1.1 Potential Benefits to the Subjects

- There are no anticipated benefits to participating in this study.
- One potential benefit would be reduced pain and reduced need for postoperative opioid medications, if in the intervention arm.
- If in the control arm, one potential benefit would be to contribute to generalizable knowledge. There would also potentially be benefit from the regular bupivacaine over the standard of care which does not include administration of bupivacaine via surgical TAP block.

12.1.2 Known Potential Risks & Risk Minimization

12.1.2.1 Procedural Risks

- There is a risk of loss of confidentiality. Measures will be taken to prevent loss of confidentiality as described in sections 11.3 Handling of Data to Ensure Confidentiality and 11.5 Data Confidentiality.

12.1.2.2 Interventional Risks

- There are risks of allergic reaction to regular bupivacaine HCl or liposomal bupivacaine. There are also risks of adverse reactions as delineated above. Subjects with a known allergic reaction to bupivacaine of any type will be excluded. Measures, such as aspirating to avoid intravascular injection, will also be taken to avoid adverse reactions.

12.1.2.3 Risk Minimization

Described below is the rationale for the necessity of exposing subjects to risks and a summary of the ways that risks to subjects were minimized in the study design

- Subjects with a known hypersensitivity or allergy to bupivacaine will be excluded
- Regarding loss of confidentiality, paper CRF forms and ICF documents will be stored in a locked cabinet in the locked research coordinator's office.
- Online data will be stored only in secure online servers such as REDCap and Meriter's secure server.

The risks of participation in the study outweigh the value of the information to be gained. The risks of participation in this study are overall minimal as we will not enroll patients with a known hypersensitivity or allergy to bupivacaine. There is a potential benefit of pain reduction if the subject is in either arm of the study compared to the standard of care which is to not administer any local anesthetic drugs via surgical TAP block.

12.2 Unanticipated Findings

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the informed consent documents, the Investigator's Drug Brochure) and the characteristics of the subject population being studied. An event may be considered

unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.
- The incidence, experience, or outcome is related to or probably related to participation in the research study. Probably related means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.

The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

12.2.1 Adventitious Findings
No imaging studies will be obtained as part of the protocol for this study; therefore, we do not anticipate any adventitious findings. Other study results will not be reviewed for adventitious findings.

12.3 Clinically Significant Findings
If there are clinically significant findings that occur during the course of this study, they would usually be discovered as part of routine prenatal or postpartum care. Subjects may request this information from the lead researcher.

A copy of all notifications provided to the subject is maintained in the subject's research file.

12.4 Findings of Unknown Significance
No findings of unknown significance are anticipated as we are not collecting specimens for analysis.

A copy of all notifications provided to the subject is maintained in the subject's research file.

12.5 Adverse Event (AE) Definition
Adverse event (AE) means any untoward or unfavorable medical occurrence in a human subject or others that happens during or after participation in a research study.

12.6 Serious Adverse Event (SAE) Definition
- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - **Does NOT include usual post-partum hospitalization of 2-4 days post-operative stay)**
    - DOES include post-op stay >4 days
    - DOES include re-admissions after the usual postpartum hospitalization
- Results in a persistent or significant disability or incapacity
- Results in congenital anomaly/birth defect: note, the study drug used in this study would be administered after delivery of the neonate
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

12.6.5 Severity of Event
All AEs will be assessed by the clinician using [specify the defined grading system, e.g., the Common Terminology Criteria for Adverse Events (CTCAE), each event searchable using the Safety Profiler website (https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx). For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild (grade 1)** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate (grade 2)** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe (grade 3)** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
- **Life threatening (grade 4)** - The patient was at risk of death at the time of the event.
- **Fatal (grade 5)** - The event caused death.

12.6.6 Relationship to Study, Study Procedure(s) and/or Study Intervention(s)

For all collected AEs, the clinician who examines and evaluates the subject 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.

- **Definitely Related** – Clearly related to the study procedures/intervention and other possible contributing factors can be ruled out.
- **Probably Related** – Likely related to the study procedures/intervention and the influence of other factors is unlikely.
- **Possibly Related** – Possibly related to the study procedures/intervention and there are other factors that could be equally likely.
- **Unlikely to be related** – Doubtfully related to the study procedures/intervention and there is another likely cause.
- **Unrelated** – Clearly not related to the study procedures/intervention and/or evidence exists that the event is definitely related to another cause.

12.6.7 Expectedness for Study, Study Procedure(s) and/or Study Intervention(s)

The PI will be responsible for determining whether an AE is expected or unexpected in relation to the study procedures and intervention(s) (as applicable).

For investigational drug and device studies, an AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, device manual, investigator's brochure, investigational drug brochure, the package insert(s), the IRB application, or the informed consent document. Expectedness is recorded for both study procedures and interventions.

For studies not evaluating an investigational drug or device, an AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, the IRB application, or the informed consent document. The expectedness could be based on study procedures or the characteristics of the patient population.

12.7 Documenting and Reporting of AEs, SAEs & Ups

12.7.1 Documenting AEs, SAEs & Ups

Adverse events will be identified by review of the electronic medical record or inquiries with subjects or concerns from the nurses on the postpartum floor on a weekly basis or as needed when concerns are raised by nurses or subjects. Study subjects will be instructed to contact the research coordinator or PI (K. Antony) if any serious or unexpected adverse event occurs. Adverse events will be discussed at weekly research team meetings and will be reviewed to determine whether a change in protocol is necessary.

An abnormal laboratory result will not be assessed as an AE unless that result leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be clinically significant.

For the purposes of this study, baseline comorbid conditions will be documented prior to the administration of the study intervention. Only those symptoms identified as new or worsened compared to the baseline assessment and not related to the obstetric course will be recorded as an AE.

AEs will be documented on the appropriate case report form.

12.7.2 Reporting AEs, SAEs & Ups

AE/SAEs that meet the definition of an unanticipated problem will be reported to the IRB within 14 business days of learning of the event. Events that are immediately life threatening, severely debilitating to other current subjects or resulted in a death will be reported to the IRB Chair or IRB Director via telephone or email within 24 hours (1 business day) of site awareness.

All AEs will also be reported to the ICTR DMC by completing the AE/SAE forms in ICTR REDCap and will be reported within the same timeframe as required by the IRB. The DMC co-chairs will review any reported SAE and if needed, schedule an ad hoc meeting of the full committee.

12.8 Stopping Rules

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency and the regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and DMC and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

13. Study Analysis

13.1 Statistical Hypothesis

- Primary Efficacy Endpoint(s):
  - To determine whether liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery will reduce the total dose of opioids received.
  - *Hypothesis:* Our hypothesis is that liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery will reduce the total dose of opioids received in 48 hours.
  - Developmental SubAim: If liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery does reduce the total dose of opioids received, to determine the degree of the reduction in order to allow for an adequately powered randomized-controlled trial.
  - This will be tested by converting all doses of opioids received into oral morphine equivalents, calculating the total dose of opioids received in the first 48 hours, and comparing the mean and standard deviation of both groups to determine whether less opioids are used and, if so, what the expected effect size would be.

- The null hypothesis is that there would be no difference the total dose of opioids used in the first 48 hours after Cesarean delivery between the subjects randomized to the control injection and subjects randomized to the intervention injection.

- Secondary Efficacy Endpoint(s):
- To determine whether liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery will reduce patient-reported pain scores and opioid-related side effects.
- *Hypothesis:* Our hypothesis is that liposomal bupivacaine administered via surgical TAP block at the time of cesarean delivery will reduce patient-reported pain scores and opioid related side effects.
- Patient related pain scores will be compared using the Numeric rating scale (NRS) which rates pain on a 0-10 scale.
- Opioid-related side effects will be summed into a composite “Opioid side effects” outcome which will either be present or absent and Chi-Square will be used to compare the incidence of these events between groups. Individual components of the composite outcome will also be assessed.
- The null hypothesis is that the patient related pain scores and the rate of opioid related side effects would be the same between the two groups.

13.2 Sample Size Justification

This is a pilot study; therefore, sample size is based on effect size estimation of liposomal bupivacaine administered via surgical TAP block in reducing post-operative opioid use. With 25 evaluable subjects per group we will have a 95% confidence interval precision around the effect size of +/- 60% of a standard deviation. This will give us adequate precision in our effect size estimate to move forward with a larger randomized clinical trial. In order to account for up to 20% dropout, we will seek to randomize 60 participants (30 per arm).

Within two years we should feasibly be able to recruit 60 women. The limitation will be that the procedure can only be performed by providers trained in administering a surgical TAP block.

13.3 Statistical Methods

The primary outcome of total opioid dose (in OME) will be compared via Student’s t-test or Mann-Whitney U test if the distribution is non-normally distributed, and additional outcomes will be assessed via Student’s t-test, Chi-squared, or non-parametric tests, as appropriate. Statistics will be performed by Scott Hetzel with biostatistics. Analysis will be by intention to treat.

No interim analysis is planned. This drug has been demonstrated to be safe, and there is a data safety monitoring committee who will review any significant adverse events. The data safety monitoring committee will also advise on whether early termination of the study is appropriate.

Regarding missing, unused, or suspected spurious data, there will first be an attempt to validate this data via the electronic medical record. If it can be validated, the data will be used. Similarly, data points that are missing will be sought in order to have as complete a data set as possible. Otherwise, ongoing missing variables will be tabulated as missing.

13.4 Planned Interim Analysis

No interim analysis is planned. This drug has been demonstrated to be safe, and there is a data safety monitoring committee who will review any significant adverse events. The data safety monitoring committee will also advise on whether early termination of the study is appropriate.

14. Regulatory, Ethical, and Study Oversight Considerations

14.1 Safety Oversight

We will also utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study. The UW ICTR DMC is comprised of experienced members with expertise required to oversee this study. In providing oversight for the conduct of this study, the ICTR DMC will meet biannually during the time period in which participants will have any study procedures. At these meetings, the DMC members will review protocol-specific reports created by statisticians using data pulled from the ICTR Research Electronic Data Capture (REDCap) data management tool. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. Additional meetings may be scheduled as determined by the DMC or as requested by the PI. An interim analysis of study results may be performed, and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination. Refer to ICTR DMC Charter for additional details.

14.2 Protocol Deviations

A protocol deviation is any noncompliance with the IRB approved study protocol, Good Clinical Practice (GCP), as adopted by the Food and Drug Administration (FDA), applicable federal regulations or institutional policies. All deviations from the protocol must be documented and reported as required. Notably, failure of the subject to complete the online emailed survey in study activity 3 and 4 will not be considered protocol deviations because these are to assist with assessing secondary outcomes and are not mandatory to assess the primary outcome.

14.3 Publication Plan

If deemed appropriate, timely communication with the scientific community is one of the essential functions of the PI(s) and is accomplished by the publication of manuscripts in scientific literature and oral or poster presentations at scientific meetings. The publication policy as it pertains to this is meant to be flexible and to facilitate rapid and accurate publication of results. Investigators are responsible for drafting the publications and presentations with meaningful input from study sponsors. Internal review of manuscripts and abstracts is deemed necessary to ensure accuracy and consistent representation of concepts and data from the clinical trials. The procedures outlined herein are guidelines and all publications of the must meet the criteria for authorship, disclosure, scientific integrity and other requirements of peer-reviewed scientific journals. Subject Study IDs are not to be used in any publications.

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