Appendix 1. Study Protocol

1. Background and Objectives

1.1 Importance of the Problem

Cesarean delivery is the most common inpatient surgical procedure in the United States [1]. There were 1.3 million cesarean deliveries performed in 2014, accounting for 32% of all deliveries, and representing a 60% increase since 1996 [2,3]. Prescription opioids are one of the mainstays of pain management after cesarean delivery. For many women, a cesarean delivery is her first major surgical procedure and may also be her first exposure to prescription opioids. Although opioids are an effective pain management strategy, there are associated risks and side effects, including respiratory depression, nausea, vomiting, postoperative ileus, sedation, constipation, and urinary retention, all of which have a negative impact on postoperative recovery.

In addition, there is an ongoing nationwide epidemic of prescription opioid abuse, accounting for over 300,000 emergency department visits per year [4]. Between 2000 and 2014, opioid overdoses far surpassed motor vehicle accidents as one of the leading causes of accidental death [5,6]. Moreover, opioids from legitimate prescriptions are a primary source of prescription or illicit opioids being used for recreational purposes, leading to adverse health consequences such as death from overdose [7,8]. Given the opioid epidemic, there is significant interest in refining opioid-sparing postoperative pain management strategies across a variety of disciplines.

There is a particular interest in the state of Massachusetts, which is experiencing a disproportionate burden of the opioid epidemic, with increasing rates of opioid deaths every year. To begin to combat this problem, the state of Massachusetts recently passed a law in March 2016 to restrict the prescription of a greater than 7-day supply of opioids, and the governor has made opioid abuse a top priority [9].

1.2 Post-cesarean Delivery Pain Management

The current standard of care for pain management after cesarean delivery includes long-acting intrathecal morphine, acetaminophen, NSAIDs such as ibuprofen or ketorolac, and oral opioids.

Other pain management options that have been considered to decrease post-operative pain and opioid use include transversus abdominus plane (TAP) blocks or infusions of local anesthetic into the wound. Neither strategy has been demonstrated to improve post-operative pain or decrease opioid consumption when intrathecal morphine is administered; moreover, TAP blocks are time-consuming procedures that require additional expertise from anesthesiologists that is not easily available across the United States.

1.3 Liposomal Bupivacaine

Liposomal bupivacaine (trade name, Exparel [Pacira Pharmaceuticals, Inc]), is 1.3% bupivacaine suspended in a liposomal formulation that allows for a controlled released of local anesthetic over time. The half-life of liposomal bupivacaine is 24-34 hours; therefore, the impact of local anesthetic may be up to 72 hours post-operatively.

Liposomal bupivacaine has been studied in several settings. Most similar to an obstetric population is a randomized trial comparing bilateral TAP blocks with 40cc bupivacaine 0.5% to 60cc of liposomal bupivacaine at the time of abdominal hysterectomy via Pfannenstiel incision [10]. Relevant exclusion criteria included those with current use of opioids, history of drug

addiction, current pain at the time of surgery, and contraindications to acetaminophen or NSAIDs. Intrapartum anesthetic management was standardized across both groups. Postoperative pain management was with morphine PCA with standardized settings for 24h, followed by as-needed oral opioids, and scheduled NSAIDs and acetaminophen throughout the postoperative period. The study was powered to detect a 2-point difference in the mean visual analog scale (VAS) for overall postoperative pain, from 4 to 2. The study met enrollment goals, and demonstrated improved pain scores and decreased postoperative use of IV and oral opioids, approximately 17mg less in IV morphine equivalents [10].

Other settings in which liposomal bupivacaine has been studied include orthopedic and spine surgery, robotic surgery, and hemorrhoidectomy and bunionectomy. Study designs have been both retrospective and prospective. Results have been variable, with some studies showing no difference in either pain score or opioid use, while others demonstrating clear improvement in either or both of these metrics [11,12,13,14].

Liposomal bupivacaine has not been studied in the setting of cesarean delivery, and has the potential to significantly decrease the use of opioids in a large population of women. It is currently FDA-approved to be used in any surgical site, and is also approved for women who are currently breastfeeding.

1.4 Study Aims & Hypotheses

This study is a pilot randomized trial to implement the infiltration of liposomal bupivacaine in the Pfannenstiel incision at the time of cesarean delivery.

Our aims are:

1. To measure pain scores with activity at 48- and 72-hours postoperatively after cesarean delivery
2. To measure total post-operative opioid use after cesarean delivery.
3. To measure patient satisfaction with pain control, using a validated tool
4. To describe adverse events related to liposomal bupivacaine infiltration

We hypothesize that the addition of liposomal bupivacaine to multi-modal pain management after cesarean delivery will reduce pain scores with activity at 48- and 72-hours after cesarean delivery.

1.5 Impact on Patient Care and Public Health

If the pilot study shows an impact on pain scores, or a trend towards decreased inpatient opioid use, we plan to perform a randomized controlled trial, powered on opioid use, to test this hypothesis. If this intervention is successful in reducing inpatient opioid use and improving post-operative recovery, liposomal bupivacaine may represent an important tool in improving post-operative pain management for women undergoing cesarean delivery. On an individual level, this may allow women to more readily care for their newborns. From a public health perspective, a reduction in inpatient opioid use will decrease opioid-related side effects and may translate to a reduction in outpatient opioid use, thus decreasing the risks of opioid abuse and misuse, ultimately resulting in fewer opioid-related adverse events and deaths.

2. Design and Analysis

2.1 Trial Design
This study is a randomized controlled trial. A total of 80 patients will be randomized 1:1 to intervention (liposomal bupivacaine) versus control (placebo solution).

2.2. Study Participants
Approximately 400 scheduled cesarean deliveries occur per year at Massachusetts General Hospital (MGH) in Boston, MA, an academic hospital affiliated with Harvard Medical School that serves a diverse patient population.

Inclusion criteria:
(1) Scheduled cesarean delivery via Pfannenstiel incision;
(2) Planned neuraxial anesthetic with intrathecal morphine and fentanyl administration.

Exclusion criteria:
(1) Current or prior use of methadone, buprenorphine, or other opioids before cesarean delivery;
(2) Contraindication to neuraxial anesthetic;
(3) Allergy to local anesthetic;
(4) Planned general anesthetic.
(5) Age less than 18 years on the date of enrollment

Women will not be excluded if they received general anesthesia after neuraxial anesthesia with intrathecal morphine was administered.

2.3 Intervention
The planned intervention is the infiltration of liposomal bupivacaine at the time of fascial closure at a Pfannenstiel incision, after the delivery of the infant and repair of the hysterotomy. Liposomal bupivacaine is packaged as a 20cc vial, meant to be diluted in an adequate amount of normal saline (NS) to provide a block in the surgical field. The adequate amount of liposomal bupivacaine/NS mixture for a Pfannenstiel incision at the time of cesarean delivery is not known.

In the previously described study for abdominal hysterectomy via Pfannenstiel incision, a total of 60cc was infiltrated in the field. The Pfannenstiel incision for a hysterectomy is smaller than a typical Pfannenstiel incision at the time of cesarean delivery; thus more volume is likely to be needed to perform an adequate field block. In one of the investigator's prior institutions, 20cc of liposomal bupivacaine was diluted into 60cc NS, for a total of 80cc infiltrated. This is the volume we will instill in the current study, given prior experience with this infiltration volume.

The total 80cc will be divided in to 4 20cc syringes with a 22G needle. The dilutions and aliquoting into the syringes will be performed by the injecting clinician.

The procedure to instill the drug is as follows: Once the patient is in the operating room, neuraxial anesthesia will be administered per routine practice. A Pfannenstiel skin incision will be made. The usual cesarean delivery procedure will be performed at the discretion of the surgeon. Once the surgical team is about to begin fascial closure, the study drug will then be infiltrated by a member of the study team (WHB, BJW, MP, or MAC – all of whom are obstetricians and trained in drug infiltration), with 50% of the study solution in subcutaneous

space and 50% in the fascial plane, taking care to evenly spread the drug in the superior and inferior aspects of the incision. For the fascial infiltration, liposomal bupivacaine will be preferentially infiltrated laterally. The remainder of the cesarean delivery will proceed according to the usual fashion. We recommend suture closure for a subcutaneous wound > 2cm and suture closure of the skin, as both of these are evidence-based practices to decrease wound complications. We also recommend not using Mastozol for improved application of steri-strips. At any point in the cesarean delivery, the surgeon may chose to administer or withhold ketorolac.

Post-operative pain management will be: intrathecal morphine, scheduled ketorolac 30mg IV x 24h followed by ibuprofen 600mg q6h x 24h, scheduled Tylenol 650mg q6h x 48h, and prn oxycodone 5-10mg q4h. This is the current pain management protocol for postoperative women after cesarean delivery. If Tylenol or NSAIDs are contraindicated, either due to the discretion of the clinical team or pre-existing patient contraindication, these will not be administered but are not a reason for study exclusion. After the first 48 hours of scheduled NSAIDs and Tylenol, these medications will be available as needed for additional pain control.

2.4 Control

The MGH Research Pharmacy will provide a placebo solution of 20cc of sterile normal saline, as there is no solution that is truly a mimic of liposomal bupivacaine in terms of viscosity and opacity. This was decided after meeting with the MGH Research Pharmacy. For patients enrolled in the control group, 80cc of saline will be infiltrated in the same manner as described above. The injecting clinician will not be blinded as to which solution the patient received, but the patient, treating clinicians, and remainder of the study team, including the outcome assessor, will remain blinded. Post-operative pain management will also proceed as above.

2.5 Outcomes

The primary outcome is pain score with activity at 48-hours and 72-hours postoperatively. A visual analog scale will be shown to the patient at both time points.

Additional outcomes to be collected from the participants include:

1. Total opioid use, converted to morphine milligram equivalents using this converter (http://www.globalrph.com/narcotic.cgi) at 48- and 72-hours postoperatively. This will be abstracted from the chart.
2. Satisfaction with post-operative pain control, using a validated tool (Pain OUT)
3. Opioid-related adverse events: nausea, vomiting, urinary retention, dizziness, drowsiness, based on patient self-report.
4. Post-operative pain at 24 hours postoperatively, using validated pain scale
5. Pre-operative anxiety, using validated tool (GAD7)
6. Planned mode of feeding (antepartum), and actual mode of feeding upon discharge and at 6 weeks postpartum
7. Adverse wound complication, through chart abstraction and follow-up phone call at 6 weeks postpartum
8. Leftover opioids in the home, at 6 weeks postpartum

Additional outcomes to be collected through medical record abstraction include:

1. Hospital length of stay.
2. Inpatient or outpatient (followed for 6 weeks from delivery) wound complication (breakdown, seroma, hematoma, infection). This is already recorded in the medical record.

3. Allergic reaction attributable to local anesthetic. This is already recorded in the medical record.
4. Local anesthetic toxicity. This is already recorded in the medical record.Operative time of cesarean delivery (skin incision to skin closure). This is already recorded in the medical record.
5. Number of oral opioids provided upon discharge. This is already recorded in the medical record.

2.6 Sample Size

We plan to enroll 80 patients into this pilot study, 40 per group. This sample size is based on prior data among women who had a cesarean delivery at MGH, and were asked to report their pain scores with activity at 48- and 72- hours after operation. With this sample size, we have 80% power to detect a 1.5 point difference in pain at 48 hours, and 90% power to detect a 1.5 point difference in pain at 72 hours. See the power table below.

Outcome	Mean	SD	Effect size	Sample size (per group), 80% power	Sample size (per group), 90% power
Δ pain with activity at 48h postop	5	2.1	Δ 2 pt	18	24
			Δ 1.5 pt	**31**	42
			Δ 1 pt	70	93
Δ pain with activity at 72h postop	3.8	1.8	Δ 2 pt	13	17
			Δ 1.5 pt	23	**31**
			Δ 1 pt	51	68

As the time point for intervention will occur immediately after confirming consent, and the impact of follow-up is minimal, we do not anticipate significant loss to follow-up.

2.7 Randomization

2.7.1 Sequence Generation

Study patients will be allocated 1:1 between intervention and placebo group, in randomized blocks of 2-6, stratified by type of cesarean delivery (primary or repeat cesarean delivery). The sequence will be generated by the MGH Research Pharmacy.

2.7.2 Allocation Concealment

Information regarding allocation to treatment groups will remain with the MGH Research Pharmacy. At the end of all study enrolment, concealed data (labeled with group numbers) will be transmitted to the statistician. Once analyses are complete, allocation will be revealed to the analysis team.

2.7.3 Implementation

Study participants will be randomized by the MGH Research Pharmacy upon signing consent to enter the study. At the time the patient presents for delivery, the pharmacy will have either the liposomal bupivacaine 20cc vial, or 20cc of sterile normal saline ready for pickup by the injecting clinician. The injecting clinician will then mix the intervention or control solutions, and divide into the appropriate number of 20cc syringes. These syringes will be marked as "Study Drug." This will occur on Labor and Delivery, in the operating room. Per the manufacturer, there can be up to a 4h delay between drug mixing and infiltration, thus allowing for unanticipated last-minute delays in case start time.

2.7.4 Blinding

Intraoperatively, study patients, the treating surgical team, anesthesiologists, and OR staff will be blinded as to the contents of the study drug. The injecting clinician, having prepared either the study drug or saline placebo, will be aware which drug the patient is receiving. The obstetricians (WHB, BJW, MP, MAC) in the study will be involved in study recruitment, informed consent, drug infiltration, and will perform the post-operative outcomes assessment, as will a research coordinator. However, the individual performing the drug infiltration will not be the individual performing the outcomes assessment. One of the investigators will perform the statistical analysis on concealed data, without identifying patient information. None of the investigators will be involved in the clinical care of the study patients during their delivery admission.

2.8 Statistical Methods

Descriptive statistics will be used to summarize pain scores at 48 and 72 hours in both the placebo and intervention groups. Similarly, mean total opioid use at both time points will be summarized. The mean opioid use and variance within each group will be used to estimate an effect size for a fully powered trial based on opioid use. The means will be compared by the t-test or a non-parametric test, depending on the distribution of the data. Categorical outcomes will be compared by chi-square or Fisher's exact as appropriate: satisfaction with pain control, adverse events, and the other outcomes listed above. No interim analyses will be performed once the randomized trial has begun.

3. Study Procedures

3.1 Recruitment Strategy

All obstetric providers (physicians, midwives, clinic nurses, labor nurses, postpartum nurses) at MGH will be made aware of this study.

One study physician (MP) will identify patients with scheduled cesarean deliveries and contact the patient's primary provider to inform the patient that this study physician will approach them about the study. If the patient's primary provider feels the patient is not an appropriate study candidate, or the patient declines to hear about the study, the patient will not be approached by the study physician. A flier will be used to educate patients in outpatient obstetric clinics about the study.

If the patient agrees to hear more, she will be approached by a study physician during a routine clinic visit 1-6 weeks before the scheduled surgical date, or contacted via phone to set up a time to meet in person. At this visit, a member of the study team will describe the standard of care, the intent of the study, and the potential risks and benefits. If a patient desires to enroll, informed consent will be obtained. If the patient is unable to meet with a study physician before her scheduled surgery, the consent discussion may occur remotely via phone conversation. At the time of presentation for cesarean delivery, desire to participate in the study will be affirmed. Patients with scheduled cesarean deliveries who we are unable to approach prior to the scheduled surgical date will not be approached on the day of admission.

For non-English speaking patients, they will be approached with an in-person interpreter in the outpatient setting to discuss the study, and will sign a short-form consent after reviewing the full English consent form, verbally translated with the interpreter.

For English speaking patients who are unable to meet in person prior to the scheduled surgical date, but who have heard about the study over the telephone and would like to participate, we will pursue phone recruitment and consent if the following conditions can be met: (1) have a means to receive and return the consent form electronically; (2) have the time to go through each section of the consent form with the study physician on the phone; (3) affirm their comfort with English as the primary language. If this is possible, an email will be sent securely with "send secure" in the subject line. The faxed/emailed back copy will be printed in the chart, with the consenting study physician signing the copy upon receiving it, and the patient will be requested to bring their version on the scheduled surgical date so that the same study physician can sign the consent form. A note will be made in the chart regarding the patient's participation and phone consent.

There will also be recruitment fliers posted in the outpatient clinic restrooms, as this is the designated space in the outpatient clinic for all recruitment fliers for research studies.

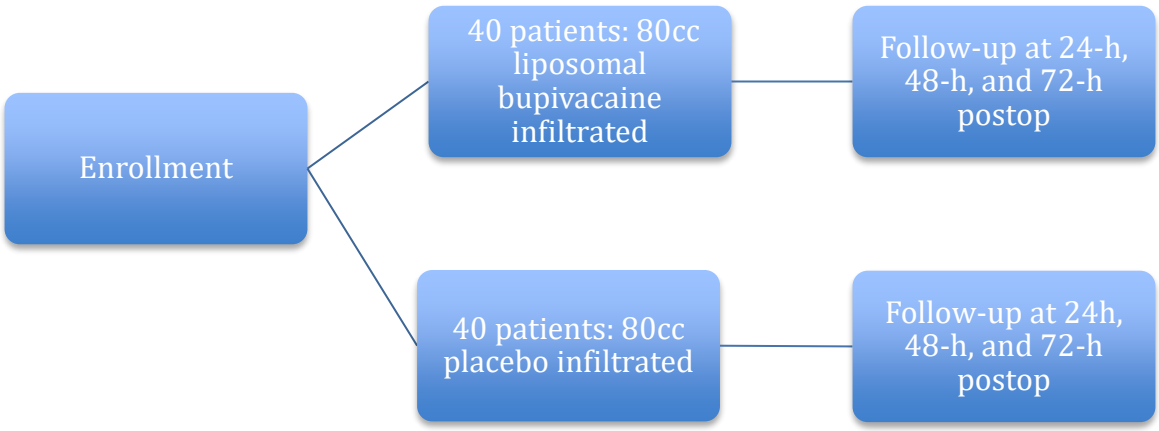
The study has been named the PENGUIN study, for ease of remembering for patients and providers alike. Postperative pain: Exparel iNjection with the Goal of Understanding the Impact on Numeric Pain Score. Cartoon penguins are pictured on the recruitment flier.

3.2 Administration of Intervention

Upon a study patient's arrival to Labor and Delivery, the MGH Research Pharmacy will be notified. The pharmacy will then have the study drug or saline placebo, based on the patient's randomization number, ready for pickup by the injecting clinician.

WHB, BJW, MP, or MAC will be responsible for infiltrating study drug at the time of the cesarean delivery. Each of these individuals is an obstetrician.

See flow chart below.



3.3 Data Collection

Baseline data, collected from the patient

(1) Demographic and socioeconomic information (race/ethnicity, insurance).

Baseline data, collected via chart abstraction

(1) Medical and surgical history.

Intraoperative data –

(1) Length of surgery;
(2) Primary vs repeat cesarean delivery;
(3) Intraoperative complications;
(4) Type of anesthetic administered.

Inpatient postoperative data. Outcomes as listed above in Section 2.4. This will be collected both via chart abstraction and via short interviews with study participants.

As close as possible to 24, 48, and 72 hours after cesarean delivery, study participants will be approached to ascertain the following:

(1) Current pain score with activity
(2) Any opioid-related adverse outcome

(3) Any wound complication or concern
(4) Satisfaction with pain control (using PAIN OUT tool) (at 48h only)
(5) Breastfeeding habits and intentions

At all timepoints, we anticipate the questions to require approximately 10 minutes.

Outpatient postoperative data, through chart abstraction:

(1) Number of oral opioids provided upon discharge
(2) Follow-up visits for wound concern over the first 2 weeks post-operatively
(3) Wound complications over the first 2 weeks post-operatively

Outpatient follow-up, through follow-up phone calls:

(1) any self reported wound complications (corroborated through MGH chart as applicable)
(2) leftover opioids from prescription after cesarean delivery
(3) satisfaction with overall pain control after cesarean delivery
(4) current mode of infant feeding

3.4 Study Timeline

1) IRB review: 12 weeks
2) Preparation of all study materials (data collection forms): 4 weeks
3) Recruitment and implementation: 24 weeks
4) Data analysis and draft manuscript preparation: 16 weeks

3.5 Staff Requirements

(1) Study physicians (WHB, BJW, MP, MAC) will be responsible for recruiting patients and will be the physicians infiltrating liposomal bupivacaine at the time of cesarean delivery.
(2) Two study physicians (MP, EMH) and a research coordinator will be responsible for post-operative patient-level outcome data, medical record chart abstraction, database creation into Redcap, and data entry into Redcap
(3) MGH Research Pharmacy will be responsible for storing the vials of liposomal bupivacaine, randomization, and allocation concealment.

3.6 Data Management

Data will be stored in a locked room, in a locked filing cabinet. Only members of the study team will have access to this data. Once the data is transcribed to a database, this will be a password-protected database. Data will be de-identified.

3.7 Monitoring and Quality Assurance

As this is a small trial, we do not plan an external committee to monitor outcome data. One study physician (MP) will receive all safety reports. There will be no interim analysis of primary outcome data. However, safety and adverse event data will be reviewed by 1 study physician as the events occur. If >20% of patients have a wound complication (approximately three times our normal rate), the study team will gather and terminate the study early. Adverse events will be reported in accordance with the CONSORT extension to better report trial harms. The adverse events of interest include any local anesthetic allergic reaction, wound complication, and opioid-related side effects. Unanticipated problems or harms to study subjects or others, including adverse events, will be reported to the IRB, in accordance with the guidelines *Reporting Unanticipated Problems including Adverse Events*.

One study physician (MP) will primarily be responsible for adhering to this protocol, with recruitment methods, administration of intervention, and assessment of outcomes in the post-operative period. The PI (WHB) and 1 study physician (MP) will ensure the accuracy and completeness of consent forms and data entry forms. The PI (WHB), study physician, and research coordinator will meet at every 2 week intervals to discuss recruitment, study implementation, and adherence to study protocol. The study team will be blinded to the intervention performed until the groups are revealed by the Research Pharmacy after the analysis is complete.

4. Benefits and Risks

4.1 Benefits

Potential benefits to participating individuals include improved pain control in the immediate post-operative period, thus resulting in fewer opioids used. This may lead to other benefits, including earlier ambulation, earlier return of bowel function, possibly earlier readiness for discharge.

Potential benefits to our patient population include the possibility for increasing opioid-minimizing strategies for pain management after cesarean delivery, the most common surgery performed in the U.S.

4.2 Risks and Discomforts

Potential risks include increased bleeding in the subcutaneous space or subfascial space, with infiltration of liposomal bupivacaine to create a field block. If this bleeding were to occur, it is not likely that it would be concealed and lead to an unanticipated hematoma; however, additional hemostatic measures may be necessary. These measures are commonly employed at cesarean delivery, even in the absence of infiltration of a substance, as these are areas that are at risk of hematoma formation. To minimize this risk, we will ensure adequate hemostasis prior to subcutaneous space closure.

Another potential intraoperative risk is increased operative time. We anticipate that the time needed to complete liposomal bupivacaine infiltration is approximately 2-3 minutes. However, if a patient's regional anesthetic is inadequate to complete surgery, additional anesthetic may need to be administered to account for the longer operative time. One surgeon will perform all infiltrations both to standardize the procedure and to minimize time spent performing the infiltration.

Post-operatively, the risk of wound complication may be increased by the infiltration of additional fluid near the incision. There is no reported data to support this concern in the prior study of liposomal bupivacaine during abdominal hysterectomy.

After enrollment, we may discover the patient has untreated anxiety, based on the GAD7. If the score suggests significant anxiety (GAD7 score >=10), we will alert the patient's primary obstetrician.

Finally, potential risks include a small amount of bupivacaine entering the breastmilk. Although the goal of this formulation is for the drug to not become systemic, this may occur. Liposomal bupivacaine is FDA-approved for breastfeeding women. Moreover, bupivacaine ingested into a neonate's gut cannot be absorbed systemically, thus minimizing the risk to the neonate.

Psychosocial risks include creating an expectation of improved pain control that may not be borne out, either because the patient may receive the placebo, or because liposomal bupivacaine may not be effective.

In addition to the risks above, there may be additional unanticipated risks to subjects or other persons that are encountered through the course of this study. We will monitor subjects and other persons for unanticipated problems, including adverse events, and if these occur, they will

be reported to the Partners Human Research Committee/IRB, in accordance with the guidelines *Reporting Unanticipated Problems including Adverse Events*.

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