Transdermal Lidocaine Patch for post-Cesarean pain control for women with obesity: a single-blind randomized controlled trial

The OBstetric Lidocaine Patch (OBLido) Trial

Protocol Number: [2018-015]

Principal Investigator: Kathleen M. Antony, MD, MSCI

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Protocol Version History

Protocol Version	Version Date	Brief description of protocol modification/actions requested, if any
Version 0.0		
Version 1.3	01-17-2019	Initial Review approved protocol

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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
Kathleen M. Antony	Kathleen M. Antony	005-08-2019
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
EMR	Electronic Medical Record
ePDMP	Prescription Drug Monitoring Program
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

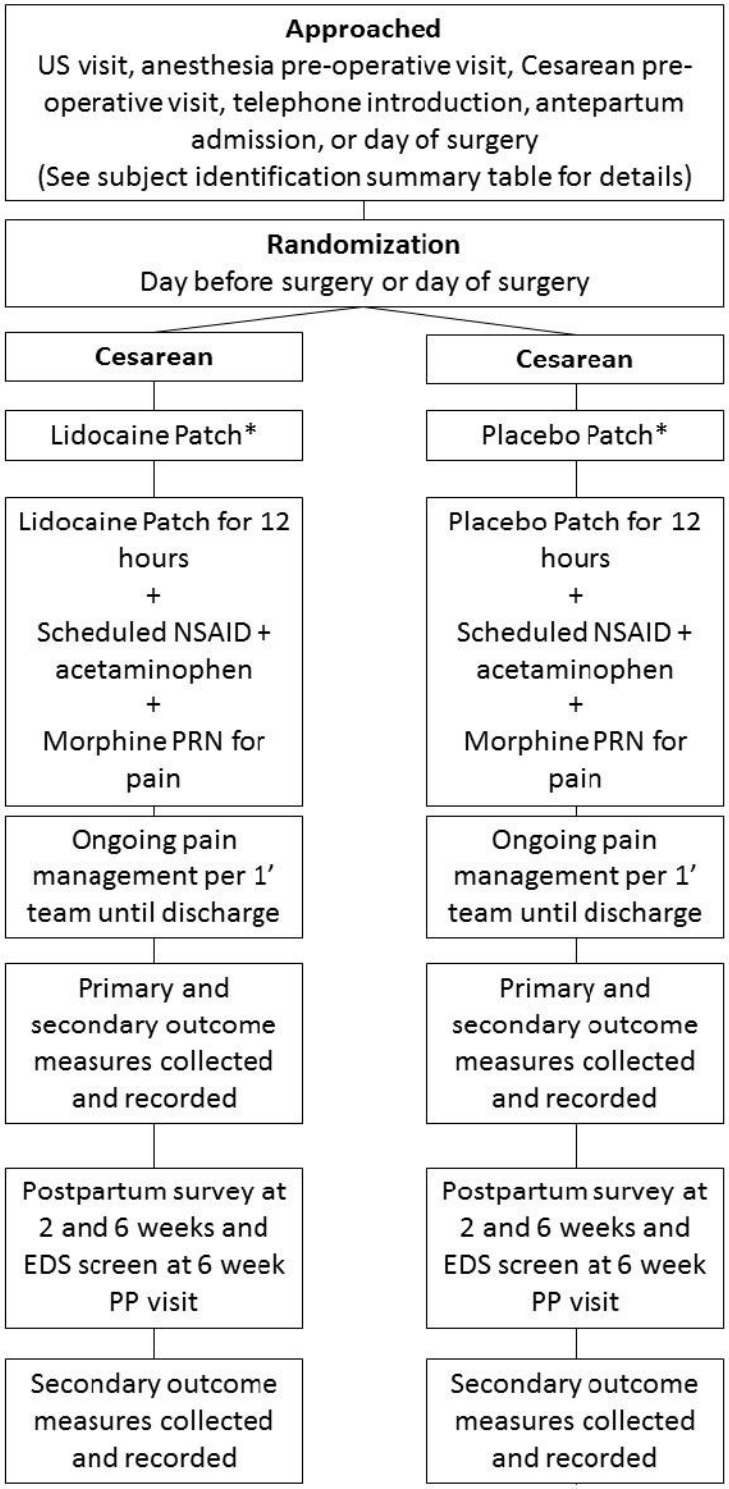
3. Study Summary

3.1 Synopsis

Title	*Transdermal Lidocaine Patch for post-Cesarean pain control for women with obesity: a single-blind randomized controlled trial*
Protocol Number	UPH-Meriter IRB #2018-015
ClinicalTrials.gov Identifier	NCT03810235
Number of Site(s)	Single center
Main Inclusion Criteria	○ Prepregnancy body mass index ≥30 kg/m^2 or ≥35 kg/m^2 at delivery if no prepregnancy/ early pregnancy weight available ○ 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 ○ Gestational age greater than or equal to 32 weeks ○ Maternal age greater than or equal to 18 years ○ Able to consent in English
Main Exclusion Criteria	○ Known hypersensitivity to lidocaine or colloid patch (defined as a history of a reaction or allergy to lidocaine (injectable, intravenous, or transdermal) or hydrocolloid patch reported by patient or documented in the medical record) or patient report ○ 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 24 hours postpartum ○ Unable to receive regularly scheduled postpartum analgesics such as acetaminophen, ibuprofen, ketorolac or any other analgesic in the UPH-Meriter formulary.
Primary Objective	To reduce the total dose of opioids received in the first 24 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 with prepregancy obesity undergoing scheduled Cesarean delivery at UnityPoint-Health Meriter will be eligible.

Study Intervention	The study intervention will consist of applying two 5% lidocaine patches (or hydrocolloid placebo patches) around the Cesarean delivery incision. These will remain in place for 12 hours and will then be removed.
Total Number of Subjects	60 Subjects
Study Population	Pregnant women undergoing scheduled Cesarean delivery who have a prepregnancy BMI ≥30 kg/m^2 or ≥35 kg/m^2 at delivery if no prepregnancy/ early pregnancy weight available.
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 the Dr. Richard Chappell, PhD.
Estimated Enrollment Period	12 months from initial subject enrollment
Estimated Study Duration	12 months from initial subject enrollment

3.2 Schematic of Study Design



*See expected study drug schedule table for details

4. Key Roles

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

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5. Introduction

5.1 Background

Obesity is the most common co-morbid condition of pregnancy and is increasing in frequency.(1) Over the last year, UnityPoint-Health Meriter has committed to improving the outcomes for obstetric patients with obesity via the creation of the Bariatric Obesity Taskforce and the "Care of the Bariatric Obstetric Patient" clinical care guideline. This is critical because obesity is associated with adverse pregnancy outcomes including increased risks of gestational diabetes, hypertensive disorders of pregnancy, fetal macrosomia, and notably, Cesarean delivery (both scheduled and unscheduled).(2,3,12,4–11) Pain control after Cesarean delivery in obese patients can be a challenge, particularly when co-morbid conditions such as sleep apnea or hypertension are present, as these conditions can limit safe pain control options.(13,14) Specifically, obesity increases the risk of opioid-related respiratory depression, particularly when complicated by sleep apnea, which is a common co-morbidity in obesity.(13,15,24,25,16–23) While the etiology of this risk is not yet fully elucidated, it appears that the potency of opioids in this population may be increased,(26) and patients with morbid obesity also depend more on intercostal accessory muscles to aid with respiration, and these muscles may be disproportionately affected by opioids.(27) 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,(28) so efforts to decrease the total dose may decrease the frequency of such events.

Additionally, 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, thus efforts to reduce opioid exposure postoperatively may reduce the potential for addiction.(29,30) 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.

Studies in gynecology and general surgery literature have demonstrated benefit in the use of transdermal lidocaine patches for postoperative pain control (31–36)). Previous work has shown the benefit of local wound infiltration with topical anesthetics to decrease postoperative pain scores in patients undergoing cesarean delivery. The use of lidocaine has been studied in both pregnancy and breastfeeding and has been determined to be safe as lidocaine is excreted in very small amounts in breastmilk and not thought to have any ill effects on newborns. (37–41)

Risks of transdermal lidocaine include local burning, nausea, dizziness, drowsiness, serious skin reactions such as blistering, confusion, blurred vision, ringing in the ears, and allergies and hypersensitivities. We will exclude patients with known allergies or hypersensitivities to lidocaine. Serious adverse events will be tracked as described elsewhere. Topical amide anesthetics such as lidocaine have been used in their injectable form for surgeries and procedures for decades, and the risks are well known. Lidocaine patches can be safely cut and placed in order to distribute the anesthetic in the desired area. (46) This will decrease the amount delivered in a single area in order to have greater distribution, but will not affect the safety or efficacy of the medication delivery system.

There is strong interest in pursuing this intervention at our institution. Collaborators in the department of anesthesia and nurses on the labor and postpartum floors are eager to use this medication as an attempt to decrease post-operative opioid use, particularly given the risk of opioid-associated post-operative respiratory depression in this population.(13,15,24,25,16–23). 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 multimodal analgesic methods to further reduce opioid use in the obese obstetric population and its related morbidity. Future efforts will also seek to optimize intraoperative and perioperative care of this 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 with a prepregnancy body mass index of 30 kg/m^2 or higher who are pregnant with a singleton pregnancy and who will be delivered via Cesarean delivery.

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. Obese patients are more susceptible to opioid-related respiratory depression, either due to increased potency of the medications themselves or increased dependence on accessory muscles for respiration.(26,27) Additionally, patients can become addicted to opioids following treatment of acute post-Cesarean pain.(29,30) Since 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. (28) 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, and some of which cannot.(42)

This study seeks to identify whether the use of a lidocaine patch applied around a Cesarean incision will reduce the cumulative opioid dose in the first 24 hours after surgery. The lidocaine patch will be utilized in addition to the current standard of care, which at UnityPoint-Health Meriter consists of ibuprofen, acetaminophen, and morphine and hydromorphone as needed. This study also is novel in targeted parturients with obesity, since the need to identify an effective analgesic agent in this population is particularly acute.

If successful, this pilot randomized controlled trial will be used to justify a larger randomized controlled trial and the effect size found here will be used to ensure that the larger randomized controlled trial will be adequately powered. If that trial is successful, lidocaine patches may be added to the post-Cesarean analgesia regimen utilized at UnityPoint-Health Meriter/ UW Madison OB/GYN and possibly elsewhere.

The transdermal lidocaine patch has been used in gynecology and general surgery, and the literature demonstrates that it is beneficial for reducing postoperative pain control (31–36). However, except for a single case report, the lidocaine patch has neither been used for pain control after open laparotomy cases or Cesarean deliveries.(43)

The 5% lidocaine patch is safe to use in the immediate post-operative and post-partum period. The transdermal route of administration limits the absorption of the drug to 3% of the dose.(44) When injected into body tissues for local anesthesia, such as for dental procedures, liposuction, or when utilized intravenously to control dysrhythmias, only a small amount of anesthetic and metabolites are secreted.(45) In the absence of an allergic response, the small amount ingested orally by a nursing infant is unlikely to case adverse effects and the American Academy of Pediatrics lists lidocaine among drugs that are usually compatible with breastfeeding.(37–41)

For the purpose of this study, two 10 x 14 cm 5% lidocaine patches will be applied simultaneously above and lateral to the Pfannenstiel incision; these patches will remain in place for 12 hours and will then be removed. The patches will each be cut in half, which is permissible per the package insert.(46) (The recommended maximum daily dose is three 5% lidocaine patches simultaneously for 12 hours.)(46) The placebo arm will receive two 10x10 cm hydrocolloid patches simultaneously applied above and lateral to the Pfannenstiel incision and remain in place for 12 hours. These patches will also be cut in half. Because the patches are different sizes and a placebo identical to the 5% lidocaine patch could not be obtained, this study will be single blind.

6. Study Objectives and Endpoints

6.1 Objectives

The purpose of this study is to determine whether transdermal lidocaine administered at the time of Cesarean delivery and for 12 hours postoperatively will reduce the total dose of opioids received. Our hypothesis is that a lidocaine patch will reduce the total dose of opioids received in the immediate 24 hours post-delivery. Secondary outcomes will include patient self-reported pain scores, patient-reported incidence of side effects, such as pruritis, development of objective complications, such as serious skin reactions (examples are acute generalized exanthematous pustolosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis), hypersensitivity, nausea, and nervousness. Other outcomes collected will include length of stay, time to first rescue analgesic medication, total dose of opioids in 48 hours, use of supplemental oxygen during hospitalization, total dose of opioids 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, and six week Edinburgh Depression Screen scores.

Neonatal outcomes such as five-minute Apgar scores and development of adverse outcomes will also be collected. We are not studying the neonate because the lidocaine patch wouldn't be expected to have an outcome on the neonate—the patch is applied after the baby is born. The neonatal "pregnancy outcomes" are not study objectives for the purpose of this study because the neonatal "pregnancy outcomes" will occur prior to any intervention related to this study occurring.

However, this data is being collected for demographic purposes. In obstetrical studies, it is customary to collect a few data points on the baby, and, in this study, a few data points are collected, such as birthweight, gestational age at birth, and Apgar scores, because stress related to neonatal status may have an impact on pain perception. For example, if more women in the placebo arm had babies born rather early with low birthweight who required intensive NICU care that could potentially impact their concern about pain or desire for strong pain medications.

6.1.1 Primary Objective:

- To determine whether 5% lidocaine patches placed around the skin incision following Cesarean delivery will reduce the total dose of opioids received in the first 24 hours after surgery.
- *Hypothesis:* Our hypothesis is that 5% lidocaine patches placed around the skin incision will reduce the total dose of opioids received in 24 hours after surgery.
- Developmental SubAim: If 5% lidocaine patches do 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 5% lidocaine patches placed around the skin incision following Cesarean delivery will reduce patient-reported pain scores and opioid-related side effects, including respiratory compromise.
- *Hypothesis:* Our hypothesis is that lidocaine patches 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 24 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.
- Frequency of patient-reported opioid-related side effects, such as pruritis, constipation, nausea, and mental clouding.
- Incidence of complications of lidocaine use, such as local burning, nausea, dizziness, drowsiness, serious skin reactions such as blistering, confusion, blurred vision, ringing in the ears, 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.
- A secondary analysis will also be performed analyzing the effect of the 5% lidocaine patch on opioid dose and pain score stratified by BMI.
- We will also analyze the overall cost effectiveness of the 5% lidocaine patch in terms of overall hospital costs.

6.2.3 Correlative endpoints

- 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)
- Neonatal outcomes, including Apgar scores, NICU admission and reason, birthweight, gestational age at delivery, and other routine neonatal outcomes.

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 with obesity prepregnancy undergoing scheduled Cesarean delivery at UnityPoint-Health Meriter will be eligible.
- The rationale for this study being a pilot randomized controlled trial is that the lidocaine patch has never been used before in cases of open laparotomy or Pfanennstiel incisions, therefore an effect size cannot be estimated from the literature.
- The rationale for this study being single blind is that a placebo patch identical to the intervention patch (5% lidocaine patch) is not available through either the patch manufacturer or any other pharmaceutical company. Because the patches are not identical, the providers will be able to identify which patch is being used.
- The patches will remain in place for 12 hours. Subjects will actively participate from the completion of their Cesarean delivery and have patches in place for 12 hours. Two and six week follow-up will also be performed.
- The study groups will consist of two arms:
  - One arm will receive the intervention patch, which is a 5% lidocaine patch.
  - The other arm will receive the placebo patch, which is a hydrocolloid patch.

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 24 hours after the lidocaine or placebo patch application. Additional outcomes will be collected at two and six weeks post-Cesarean.

8. Subject Selection

8.1 Target Study Sample Size

- After meeting with Dr. Emmanuel Sampene of biostatistics regarding this pilot RCT, 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 550. This approximates the number of women with body mass index greater than or equal to 30 kg/m2 who undergo Cesarean delivery at UnityPoint-Health, Meriter in a 12 month period. The most likely scenario is that less subjects will need to be screened. .
- 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.
- Subjects will be enrolled and randomized while pregnant. The intervention will occur immediately after delivery. 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

- Prepregnancy body mass index greater than or equal to 30 kg/m2 or ≥35 kg/m^2 at delivery if no prepregnancy/ early pregnancy weight available
- 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
- Gestational age greater or equal to 32 weeks

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 lidocaine or colloid patch (defined as a history of a reaction or allergy to lidocaine (injectable, intravenous, or transdermal) or hydrocolloid patch reported by patient or documented in the medical record) or patient report
- 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 24 hours postpartum
- Unable to receive regularly scheduled postpartum analgesics such as acetaminophen, ibuprofen, ketorolac or any other analgesic in the UPH-Meriter formulary.

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 whose BMI meets criteria for enrollment in the study
- The study coordinator will call the patient and read a prepared script about the study.
- If the patient is interested, the study coordinator will review the informed consent document during the telephone call.
- At a following clinical appointment or on the day of surgery, the research coordinator 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 receive a package of diapers at hospital discharge.
- After enrollment, there will be an in-person randomization and then the patches will be applied at the time of their hospitalization for Cesarean delivery.

- Two week postpartum follow-up will comprise questions about breastfeeding, number of opiod 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.
- The current plan is to have these questions sent using a function in REDCap that securely sends a 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]
- Any other valid reason.

Subjects who sign the informed consent form and are randomized but do not receive the study intervention will be replaced. These subjects will not count towards the N. 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. These subjects will count towards the N.

9. Study Intervention

9.1 Study Intervention Description

The study intervention will consist of applying a patch (either 5% lidocaine patch or a hydrocolloid placebo patch) above and lateral to the Pfannenstiel incision following Cesarean delivery. The patch will remain in place for 12 hours and will then be removed.

9.2 Source

The study 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 patches and has received confirmation that they can be obtained and the cost.

9.3 Packaging and Labeling

- The lidocaine patch will be supplied by Actavis US. (NDC 0591-3525-30). It is labeled “Lidocaine Patch 5%”. The package instructs the user not to store the patch outside the sealed envelope and has printed instructions on how to open the envelope, remove the transparent release liner, and apply the patch. The package inserts specifies that the patch may be cut prior to application. (46)
- The placebo patch will be supplied by ConvaTec under the brand name “DuoDerm”. It is labeled “DuoDerm” and it is a hydrocolloid patch. The package has printed instructions on how to remove the transparent release liner and apply the patch. These patches will also be cut. They do not contain drug.

9.4 Preparation
Both the lidocaine patch and placebo patch will be cut in half prior to application. No other preparation is required. The PI has corresponded with the PRC regarding obtaining these patches and has received confirmation that they can be obtained and the cost.

9.5 Storage and Stability
Upon receipt of the study intervention from the Pharmaceutical Research Center (PRC), they will be transported to and stored in a locked drug cabinet in the Meriter Center for Perinatal Care Clinic's accessible only by Dr. Antony or other clinical care staff and to be distributed by the research coordinators.
- The 5% lidocaine patch will be stored within the sealed envelope in which it is received.
- The hydrocolloid patch will also be stored in this manner.
- Measures will be taken to ensure limited access as well as measures to prevent accident damage or destruction.

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 5% lidocaine patch will be applied following Cesarean incision closure and application of sterile dressing in the operating room. The time of application will be written on the patch or placebo patch as well as documented in the electronic medical record for easy review. Patches will be removed at 12 hours following placement in accordance with preexisting medication guidelines. The patient's chart will be reviewed to ensure that the patches were placed and removed at the appropriate times. All patients in both arms will be administered additional analgesia in accordance with post-Cesarean pain control as per hospital guidelines. We expect compliance to be high as the patches will be placed in the operating room by a trained physician or nurse, however, we will document any deviation from the study protocol. The expected "Study Drug Schedule" is included in this documentation

9.7.1 Dose Schedule

	Enrolled	
	Randomization	
	Study Drug	**Placebo**
Intraoperative	Standard regional analgesia	Standard regional analgesia
Following Incision Closure and Dressing Application	**5% lidocaine patches applied per protocol around the Pfannenstiel incision**	**Placebo patches applied per protocol around Pfannenstiel incision**
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**	**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**	***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**
6 hours postop	15 mg IV ketorolac + 975 mg PO acetaminophen	15 mg IV ketorolac + 975 mg PO acetaminophen
12 hours postop	15 mg IV ketorolac + 975 mg PO acetaminophen + Remove patch	15 mg IV ketorolac + 975 mg PO acetaminophen + Remove patch
18 hours postop	15 mg IV ketorolac + 975 mg PO acetaminophen	15 mg IV ketorolac + 975 mg PO acetaminophen
24 hours postop	15 mg IV ketorolac + 975 mg PO acetaminophen + Resume usual 24 hour postoperative pain regimen	15 mg IV ketorolac + 975 mg PO acetaminophen + Resume usual 24 hour postoperative pain regimen

9.7.2 Dose Adjustments/Modifications/Delays

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

9.8 Randomization and Blinding

A randomization schedule will be created using the simple urn method for randomization with 25 subjects per arm for a total of 50 subjects. The study ID numbers will be sequentially assigned to participants on the day of or the day before their surgery by the research coordinator. Randomization will similarly occur at that time. Randomization will be achieved through the use of REDCap's randomization software. The patient/ subject will be blinded to the subject's allocation. However, because the patches are not identical in appearance, the clinical team and the study 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.

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. 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 5% lidocaine patch study intervention used for the purposes of this study is for the indication of pain control. The subjects being studied is 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 or prior to Cesarean delivery	At the time of Cesarean delivery	2 weeks postpartum	6 weeks postpartum
Location	See 10.2.1	OB triage, antepartum unit, or L&D room	Pt's home: REDCap Email message link to	Pt's home: REDCap Email message link to

		L&D OR (for Cesarean delivery)	survey Telephone reminder (If no prior response)	survey Telephone reminder (If no prior response)
Events	Consent	-Randomization (to occur day of or day before surgery) -Cesarean delivery (clinical event) -Study drug patch application x 12 hours	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. A waiver of consent will be used to identify potential subjects for eligibility prior to informed consent. These scenarios and mechanisms are described below:

General Recruitment and Enrollment Mechanism:
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. When providers perform a preoperative examination on a woman whose BMI 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.

The study coordinator will then call the patient and read a prepared script about the study. If the patient is interested, the study coordinator will review the informed consent document during the telephone call. At a following clinical appointment or on the day of surgery, the research coordinator 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.
Randomization will occur the day before the planned surgery or the morning of the planned surgery.

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 with a prepregnancy body-mass index ≥30 kg/m2 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 if the patient meets BMI criteria.)
Follow-up and Informed Consent: Research coordinators 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 will re-connect with the patient when the patient presents for their third trimester 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 will have the patient sign an informed consent document at that time. Then, 1-

3 days prior to the Cesarean delivery, the research coordinator will re-connect with the patient to confirm eligibility and desire to be in the study.

Third Trimester: Anesthesia preoperative consultation
Initial Approach: The Meriter Center for Perinatal Care does see women whose pregnancies are considered high risk, including patients of all body-mass indices. Only high-risk women see anesthesia for a preoperative consultation in clinic. We also host the anesthesiologists at our clinic who see all patients who are high risk for anesthesia complications during delivery.
The high risk population includes women with a prepregnancy body mass index ≥45 kg/m2, who have an anesthesia consultation during the antepartum period. This is a clinical protocol and is not related to this study. Women who are lower risk meet the anesthesiologist on the day of the surgery. This is the clinical protocol and not specific 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 because all women with a prepregnancy body-mass index over 45 kg/m2 by definition also have a prepregnancy body-mass index greater than 30 kg/m2 and would potentially be eligible for inclusion in the study.
Follow-up and Informed Consent: If such patients are scheduled for a Cesarean and have an anesthesia appointment, the research coordinator 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.

30-38 weeks gestation ultrasound: Meriter Center for Perinatal Care
Initial Approach: Patients undergoing a growth ultrasound examination (goal 30-38 weeks) at the Meriter Center for Perinatal Care with a prepregnancy body-mass index ≥30 kg/m2 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.
Follow-up and Informed Consent: Research coordinators 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 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 will have the patient sign an informed consent document at that time. Then, 1-3 days prior to the Cesarean delivery, the research coordinator 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. If such women are planning to delivery via Cesarean, after initial introduction by the clinical staff, they may be approached during their antepartum stay by research coordinators after the study is introduced by providers.
Follow-up and Informed Consent: The research coordinator 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.

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 with a prepregnancy body-mass index that

exceeds 30 kg/m^2. Subjects with a Cesarean delivery scheduled at or after 32 weeks of gestation will be eligible for enrollment. A clinical nurse provider introduces the possibility of enrolling in the study.
Follow-up and Informed Consent: Research coordinators will approach subjects, the study will be described to subjects, and informed consent will be obtained. 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.
The research staff will ask the provider whether she/he thinks the patient will have adequate time, and we will ask the patient if she feels that she has adequate time to consider being in the study. If a patient has been aware of this study prior to coming to Meriter and has seen the posters and brochures, she may feel that she wants to do this study if she undergoes a Cesarean even prior to knowing whether she will deliver by Cesarean. If a patient has not been aware of this study, she may require more time and even a few hours may not be sufficient.

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 will be performed as follows:

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

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
- Delivery will occur via Cesarean delivery

- Immediately after skin closure postoperatively, the lidocaine patch or placebo patch will be placed

Postpartum

- All patients receive either Study Drug or Placebo for 24 hours postoperatively in addition to scheduled ketorolac with additional opioids available PRN (See Figure 1)
- 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 time. The enrollee will then have their Cesarean delivery (clinical) and have the lidocaine patch applied. The Cesarean delivery will be performed by the clinical team as per the routine clinical protocol. Following the Cesarean delivery, the patches will be applied by the OR nurse or resident physicians involved in the case. This procedure will occur in the operating room. The estimated time required for patch application is 30-120 seconds. This procedure will occur while other anesthesia-related care tasks are taking place and will not add to the intraoperative time. 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.

To prevent the loss of a study envelope and disruption to the randomization code, the study team members will use the following plan. This plan will occur after the envelopes have been filled with all study materials, including the randomized patch. The plan focuses on any transport of the prepared envelopes as well as the careful reconciliation between each patient's randomization ID and the randomization IDs noted in the study tracker.

Before randomization, the randomizing physician or coordinator will obtain the next likely number from the study coordinator's tracker. The next number in sequence in the locked cabinet should correspond with one of the next numbers in sequence - either from the over 40 or under 40 BMI group. Additionally, the randomizing coordinator or physician will note their initials, as well as the corresponding randomization number and date on the check off form which is affixed to each patch storage box. The person doing the randomization will also note which patch the nurse removes from the envelope so that the sequence can be tracked going forward. If possible the empty, used envelope will be returned to the Research Coordinator.

Transporting additional packets from the PI's office to the CPC locked cabinet should be done by two people who count the packets together immediately prior to moving them and then immediately afterward just before placing them in the locked cabinet.

Post C-section follow-up surveys

Surveys will be emailed twice via REDCap, at 2 and 6 weeks postpartum, followed by a telephone call or text if there was no response to the emails. The surveys can be completed by the patient in the privacy of their own home. These study activities will be completed by the enrollee and if they fail to complete the survey after two 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.

The main purpose of the 2 week postpartum questionnaire is to inquire about how many opioid pills the patient has left. Questions about pain will also be asked. The survey from which the pain questions are extrapolated is intended to be administered after discharge. For both of these reasons, the most appropriate time to administer this questionnaire is around 2 weeks postpartum.

If subjects do not have email addresses, but do have access to the internet, then at the time of the telephone call, the web address for the survey will be read aloud to the subject and they will complete the survey online by typing the web address into the address bar of their internet browser. If the subject does not have an email address or access to the internet, then the survey questions will be read aloud to the subject over the telephone.

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 patch. (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 an allergic or hypersensitivity reaction to the lidocaine or placebo patch.
- Subject wishes to remove patch prior to 12 hours.
- Subject has a delayed complication from the Cesarean delivery and wishes to have the patches removed.
- If subject has a delayed complication from the Cesarean delivery requiring re-operation and the patches need to be removed for clinical reasons
- Any other valid reason.

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
- Patient self-removes the patch or the patch does not adhere to the patient's skin after two applications
- Study terminated
- If subject has a delayed complication from the Cesarean delivery requiring re-operation and the patches need to be removed for clinical reasons

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. These subjects will not count towards the N. 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. These subjects will count towards the N. 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”.

Subjects will not be informed of study results, but the results will be available to subjects. These results would not be expected to be available until 2020 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 research coordinator and principal investigator will keep a secure data set with the identifiable code. The research data set will use the subject code. 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.
- If in the placebo arm, one potential benefit would be to contribute to generalizable knowledge.

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 the lidocaine or placebo patch. Subjects with a known allergic reaction to lidocaine will be excluded.

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 lidocaine 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 lidocaine. There is a potential benefit of pain reduction if the subject is in the lidocaine patch arm of the study.

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 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

No clinically significant findings are anticipated. If there are findings that occur during the course of this study, they would be clinically relevant and would usually be discovered as part of routine prenatal or postpartum care. Subjects will be given the option of being notified of clinically significant findings by selecting the option on the informed consent form. The informed consent form also provides subjects with the option of whether they would like their clinical care provider to be informed of any clinically significant findings.
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
- 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 5% lidocaine patches placed around the skin incision following Cesarean delivery will reduce the total dose of opioids received.
  - *Hypothesis:* Our hypothesis is that 5% lidocaine patches placed around the skin incision will reduce the total dose of opioids received in 24 hours.
  - Developmental SubAim: If 5% lidocaine patches do 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 24 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 24 hours after Cesarean delivery between the subjects randomized to the placebo patch and subjects randomized to the 5% lidocaine patch.

- Secondary Efficacy Endpoint(s):
- To determine whether 5% lidocaine patches placed around the skin incision following Cesarean delivery will reduce patient-reported pain scores and opioid-related side effects.
- *Hypothesis:* Our hypothesis is that lidocaine patches 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 no sample size calculation was performed. One of the specific aims of this study is to determine the effect size (if any) of lidocaine patches in reducing post-operative opioid use. The sample size for this pilot study was determined to be 50 as per the recommendation of Dr. Emmanuel Sampene, PhD in biostatistics. In order to account for up to 20% dropout, we will seek to randomize 60 participants (30 per arm).

Year	Class I N	% of deliveries	Class II		Class III 40-49		BMI 50+	%
2013	328	23.4	187	29.3	114	31.3	30	40.5
2014	320	23	171	26.4	113	29.6	25	37.9
2015	228	23.7	119	25.5	87	30.7	17	39.5
2016	273	26	153	34	125	42	20	51

In any given year we have 17-30 C/Ds in BMI>50.
BMI 40+: About 100-150 total.
BMI 35+: About 200-300 total
BMI 30+: 450-550 total

In less than 1 year we should feasibly be able to recruit 60 women with a prepregnancy body mass index greater than or equal to 30 kg/m^2.

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 Dr. Richard Chappell, PhD. Additional planned secondary analysis will be performed to assess efficacy of the treatment by BMI strata. 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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