HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Lidocaine Patches After Cesarean Section (LPACS Trial)

Principal Investigator: Christopher Arkfeld, MD

Version Date: 3/7/2021

(*If applicable*) Clinicaltrials.gov Registration #: NCT04443569

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. Read the following instructions before proceeding: 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   The aim of this study is to investigate the impact of using lidocaine patches after cesarean section on pain control and opioid use in the immediate post-operative period. We hypothesize the use of lidocaine patches in the immediate post-operative period will lead to a decrease in the total opioid used for pain control compared to patients that do not have a lidocaine patch in place. We also hypothesize a decrease in the visual analog pain score compared to women who do not use a lidocaine patch in the immediate post-operative period following cesarean delivery.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   7/1/2020 to 6/1/2023

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   The use of lidocaine as a local anesthetic is a common and widely used in practice. Lidocaine patches can be used for localized pain control and can be placed every 24 hours. The use of lidocaine patches in post-operative patients has been reported in one case report in obstetric literature.[1] There is one study that reports decreased immediate postoperative pain when lidocaine patches were placed at laparoscopic port sites following gynecologic surgery as measured by visual analog scale score and the Prince Henry and 5-point verbal rating pain scale .[2] There have been no studies looking at the impact of lidocaine patches in obstetric surgical procedures, specifically cesarean sections.

   Cesarean sections are one of the most common surgeries in the United States. Following cesarean sections it is common to utilize opioids in the hospital and upon discharge to manage patient's post-operative pain. According to the CDC overdose deaths involving prescription opioids were five times higher in 2017 than in 1999 with over 200,000 deaths.[3] This creates an opportunity to decrease the use of post-operative opioids with the application of a lidocaine patch as an adjunctive post-operative pain management modality following cesarean sections.

   Women undergoing routine cesarean delivery typically receive regional anesthesia in one of the following forms: spinal, epidural or combined spinal epidural. This anesthesia provides for a pain free surgery and residual analgesia effects can last up to 24 hours after the procedure, even as movement and sensation begins to return. Current practice at Yale New Haven Hospital also involves the use of transversus abdominus plane blocks after the cesarean delivery is completed, which are performed by anesthesia for additional analgesia in the first 24 hours after the operation. Despite these measures, as in other surgical procedures, women require narcotic pain medicine to help control their post-operative pain in addition to other non-narcotic medications such as acetaminophen and NSAIDs.[4]

   Current pain regimen at Yale includes acetaminophen 650mg and Ibuprofen 600mg alternating every 3 hours with oxycodone 5mg or 10mg available every 6 hours for pain that is not relieved with acetaminophen and ibuprofen. Nationally, there is no standardized post-partum c-section pain regimen And historically women have been over-prescribed narcotics following cesarean deliveries.[5]

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Lidocaine patches are a common topical analgesia therapy used for localized pain control in the inpatient and outpatient setting. It's use in the postoperative period is less understood and the use of topical lidocaine patches has not been thoroughly investigated in the surgical literature. Thus far, it has been shown as an effective therapy at laparoscopic port sites following laparoscopic appendectomies. [6] It's use in obstetrical surgeries has not been studied. While lidocaine patches were not specifically studied in obstetrical patients during FDA approval, at Yale it is used in antepartum and postpartum settings. Regarding lidocaine in breastfeeding postpartum mothers; lidocaine patches have not been studied. Lidocaine given through the epidural for pain control during the cesarean delivery with a dosage averaging 183mg (ranging from 60-500mg) were found to have 860mcg/L at 2 hours after delivery, 460mcg/L at 4 hours after delivery and 220mcg/L at 12 hours after delivery. [7] This amount of lidocaine administration and presence in breastmilk is not a contraindication to breastfeeding and the amount present in breastmilk from a lidocaine patch would be presumed to be substantially lower.

Overall, the limited research on this topic making it a valuable area of research.

References:

1. Gilhooly, D., et al. (2011). "Topical lidocaine patch 5% for acute postoperative pain control." BMJ case reports(pagination).

2. Kim, J. B., et al. (2012). "Treatment for postoperative wound pain in gynecologic laparoscopic surgery: Topical lidocaine patches." Journal of Laparoendoscopic and Advanced Surgical Techniques 22(7): 668-673.

3. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at http://wonder.cdc.gov.

4. "ACOG Committee Opinion No. 742." Obstetrics & Gynecology, vol. 132, no. 1, 2018, doi:10.1097/aog.0000000000002683.
5. Bateman BT, Cole NM, Maeda A, et al. Patterns of Opioid Prescription and Use After Cesarean Delivery. Obstet Gynecol. 2017;130(1):29-35. doi:10.1097/AOG.0000000000002093

6. WooSurng Lee, KooYong Hahn, JungPil Hur, and YongHun Kim.Journal of Laparoendoscopic & Advanced Surgical Techniques.Sep 2018.1061-1067.http://doi.org/10.1089/lap.2018.0013

7. Ortega D, Viviand X, Lorec AM, Gamerre M, Martin C, Bruguerolle B. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. Acta Anaesthesiol Scand. 1999 Apr;43(4):394-7. doi: 10.1034/j.1399-6576.1999.430405.x. PMID: 10225071.
8.

9. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

All patient's that are admitted to the labor and delivery floor have a complete H&P collected at the time of their admission. This H&P will be used to evaluation co-morbid conditions, medications. All demographic information will be abstracted from the patient's EPIC medical record. The medical records of the participants will be gathered from the start of their pregnancy up to 72 hours following C-section and the information will be reviewed to determine eligibility for this study and will be used for analysis of the data. The information will include daily pain scores done by nurse staff during the hospital stay, a list of medication and all the other information from the medical record."

All patient's who receive prenatal care within the YNHH system have obstetric providers that utilize EPIC for their outpatient records as well so all demographic and medical history information will be in the chart. Patients undergoing a cesarean delivery after a trial of labor have time to be adequately consented (i.e. arrest of dilation, arrest of descent, failed induction) . Those undergoing cesarean delivery for emergent reasons (i.e. non-reassuring fetal heart tracing, fetal bradycardia, maternal compromise) will be excluded.

All patient's undergoing c-sections are at risk for pain. All patients undergoing c-sections require opioid medications after their surgery, similar to other surgical procedures where the abdominal cavity is entered via laparatomy. Many mother's express desire to use the least amount of opioids possible during their recovery. Since this is a randomized control trial we will be able to compare both groups and see if there are similar numbers of patients that did not require any acetaminophen or ibuprofen as well as looking at the primary outcome which is opioid use.

This will be a prospective randomized subject blinded controlled trial. The subjects will be randomized 1:1 by the Yale Maternal Fetal Medicine statistician at the time of enrollment using REDCap. Prearranged folders/packages will be created containing all needed materials and labeled with subject numbers. These will be distributed to the care team and will serve as the blinding mechanism for study subjects. All cesarean sections, excluding women undergoing their third or higher repeat cesarean sections or those done for emergent reasons out of a trial of labor, would be candidates for this study. Additional exclusion criteria would include women with previous abdominal hernia repairs with mesh or those women with a previous abdominoplasty. Patients will be approached and consented during the pre-operative period when presenting for scheduled surgery or at the time of consent for a non-scheduled cesarean section. The lidocaine patch would be placed on the superior-lateral aspect of the Pfannenstiel incision in the PACU prior to being transferred to the postpartum floor. The primary outcome of this study would be the total amount of narcotic, or opioid, medication that a patient receives within the first 72 hours following surgery as calculated by morphine equivalent units. The secondary outcome will be daily pain scores conducted by the nursing stuff will be done as part of standard of care and the study team will collect the results from subject medical chart or from medical documentation. The efficacy of the lidocaine patch for pain control will be based on the amount of narcotic or opioid medication used. If no opioids are used then this will be viewed as lidocaine patch providing adequate analgesia in conjunction with ibuprofen and acetaminophen.

After consenting to participate in the study the subjects will complete a pre-study questionnaire. Prior to discharge from the hospital the study subjects will be asked to complete a post-study questionnaire.

A single lidocaine patch or placebo (a bandage with gauze similar in appearance to the lidocaine patch) will be placed within 1 hour of completing the c-section. The patients are moved to the PACU within 15 minutes of completing the c-sections and after the initial set of vitals has been collected the lidocaine patch will be placed. The lidocaine patch or placebo patch will be placed on the superior aspect of the abdominal incision. The patch remains in place for 12 hours at a time. It will then be replaced every 24 hours and the

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replacement patch will be placed in the same position as the previous patch. The standard lidocaine patch formulation available at YNHH is 5% lidocaine. There is no dose adjustment based on weight because it is a local and not systemic analgesic. Patches will be managed throughout the patient's admission. Once the subject is released from the hospital their participation in the study ends.

The lidocaine patches are one sided. Lidocaine will not be absorbed through contact with the outward facing surface. When placed, the patients will be informed to let nursing staff know if it is not adherent to their abdomen and to not place the infant on the lidocaine patch. Heatpacks and icepacks are allowed to be used near the incision and lidocaine patch. The lidocaine patch will not put it on over an area with skin irritation or breakdown. If a lidocaine patch fell off during the study it would be replaced.

There are currently no restrictions for lidocaine used at the time of epidural, infusions, or local administrations in breastfeeding mothers. The amount of lidocaine in breast milk is low and the absorption by the newborn is minimal. Lidocaine is not a contraindication to breastfeeding. Of note, lidocaine is also used during newborn circumcisions further supports the safety of lidocaine. [1] With the use of lidocaine patches there is an unforeseen amount of lidocaine and lidocaine metabolites in breast milk.

Of note, patients will not be allowed to bring in additional lidocaine patches for use during the postpartum, consistent with current hospital policies. Also, patients will not be allowed to use lidocaine patches for management of other pains during the study time.

1. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Lidocaine. [Updated 2019 Jan 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501230/

10. Genetic Testing N/A ☒

A. Describe
- i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
- ii. the plan for the collection of material or the conditions under which material will be received *Write here*
- iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
- iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
C. Is widespread sharing of materials planned? *Write here*
D. When and under what conditions will materials be stripped of all identifiers? *Write here*
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
F. Describe the provisions for protection of participant privacy *Write here*
G. Describe the methods for the security of storage and sharing of materials *Write here*

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11. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

The inclusion criteria are as follows:
The subject population will be females in the immediate post-operative period following a primary or secondary cesarean section conducted under neuraxial anesthesia, which includes spinal or epidural anesthesia. The age range will be women 18-50 years old. Lactating mothers are included in this study.

The exclusion criteria are as follows:

- Any woman who has 3 or more prior cesarean sections
- History of abdominoplasty
- History of abdominal hernia repair with mesh
- Allergy to either lidocaine or adhesives used in medical tape
- Subjects who received general anesthesia for their cesarean section
- Women receiving methadone or suboxone for a history of substance abuse and women with a history of active substance use will also be excluded (opioids).
- Women undergoing emergency cesarean sections or those that receive general anesthesia.
- Concurrent anti-arrhythmic drugs
- Hepatic disease
- Underlying CNS excitation/depression to other amide local anesthetic agents,
- Methemoglobinemia (G6PD deficiency, congenital methemoglobinemia, and other unstable hemoglobin variants).
- non-scheduled emergent c sections
-

12. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☒Pregnant women and/or fetuses
☐Yale Students	☒ Females of childbearing potential	

The subjects recruited will be pregnant when signing the consent form (prior to the cesarean section) but will be postpartum during the study.

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

13. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

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Inclusion criteria will be any woman undergoing a primary or secondary cesarean section at Yale New Haven Hospital under neuraxial anesthesia.

Exclusion:

- Any woman who has 3 or more prior cesarean sections
- History of abdominoplasty
- History of abdominal hernia repair with mesh
- Allergy to either lidocaine or adhesives used in medical tape
- Subjects who received general anesthesia for their cesarean section
- Women receiving methadone or suboxone for a history of substance abuse and women with a history of active substance use will also be excluded.
- Women undergoing emergency cesarean sections or those that receive general anesthesia.
- Concurrent anti-arrhythmic drugs
- Hepatic disease
- Underlying CNS excitation/depression to other amide local anesthetic agents,
- Methemoglobinemia (G6PD deficiency, congenital methemoglobinemia, and other unstable hemoglobin variants).
- non-scheduled emergent c sections
-

14. How will **eligibility** be determined, and by whom? Write here
    Eligibility will be determined by the principal investigator and study personnel through review of the cesarean sections at Yale New Haven Hospital. The scheduled cesarean sections will be reviewed the day prior to determine eligibility. Additionally, those women who undergo a cesarean delivery following attempts at labor will also be screened for eligibility.

15. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
    The main risk of this study is loss of confidentiality even though data will be coded.

Concerns related to adverse effects:
Familial malignant hyperthermia: Many drugs used during the conduct of anesthesia may trigger familial malignant hyperthermia; not known whether amide-type local anesthetics trigger this reaction. However, standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. If familial malignant hyperthermia is confirmed, discontinue triggering agent and initiate appropriate therapy (eg, oxygen, dantrolene) and other supportive measures.
Hypersensitivity: Use with caution in patients with known drug sensitivities. Allergic reactions (cutaneous lesions, urticaria, edema, or anaphylactoid reactions) may be a result of sensitivity to lidocaine (rare) or preservatives used in formulations. Patients allergic to para-aminobenzoic acid (PABA) derivatives (eg, procaine, tetracaine, benzocaine) have not shown cross sensitivity to lidocaine.
Local effects: Irritation, sensitivity and/or infection may occur at the site of application; discontinue use and institute appropriate therapy if local effects occur. Mild and transient application site reactions may occur during or immediately after treatment with patch; spontaneously resolves within a few minutes to hours; may include blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechial, pruritus, vesicles, or the area may be the locus of abnormal sensation.
Methemoglobinemia: Has been reported with local anesthetics; clinically significant methemoglobinemia requires immediate treatment along with discontinuation of the anesthetic and other oxidizing agents. Onset may be

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immediate or delayed (hours) after anesthetic exposure. Patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, exposure to oxidizing agents or their metabolites, or infants <6 months are more susceptible and should be closely monitored for signs and symptoms of methemoglobinemia (eg, cyanosis, headache, rapid pulse, shortness of breath, lightheadedness, fatigue).
Systemic adverse effects: Potentially life-threatening side effects (eg, irregular heartbeat, seizures, coma, respiratory depression, death) have occurred when used prior to cosmetic procedures. Excessive dosing for any indication (eg, application to large areas, use above recommended dose, application to denuded or inflamed skin, or wearing of device for longer than recommended), smaller patients, and/or impaired elimination may lead to increased absorption and systemic toxicity; patient should adhere strictly to recommended dosage and administration guidelines; serious adverse effects may require the use of supportive care and resuscitative equipment; lidocaine toxicity may occur at blood concentrations above 5 mcg/mL.
Disease-related concerns:
Bleeding tendencies/platelet disorders: Intradermal injection: Use with caution; may have a higher risk of superficial dermal bleeding.
Cardiovascular disease: Use with caution in patients with severe shock or heart block.
Dermal integrity reduced: Application to broken or inflamed skin may lead to increased systemic absorption; use caution.
Familial malignant hyperthermia: May potentially trigger malignant hyperthermia; follow standard protocol for identification and treatment.
Hepatic impairment: Use caution in patients with severe hepatic disease due to diminished ability to metabolize systemically-absorbed lidocaine.
Pseudocholinesterase deficiency: Use with caution; these patients have a greater risk of developing toxic plasma concentrations of lidocaine.
Sepsis/severely traumatized mucosa: Use with extreme caution in the presence of sepsis and/or severely traumatized mucosa due to an increased risk of rapid systemic absorption at application site.

16. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
    The data will be de-identified, kept on a secure computer that is password protected.

Adverse effects of the lidocaine patch and placebo patch will be regularly screened for by the healthcare team, specifically the most common adverse effect of skin irritation will be mitigated by a daily physical exam performed by the healthcare team. If these adverse effects take place the study participant will not receive another lidocaine patch or placebo patch and will be withdrawn from the study.

17. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal Risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/a
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are

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available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for minimal risk:

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [*e.g., monthly, quarterly, etc*]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through weekly email communication and monthly meetings as they are reviewed by the principal investigator. The protocol's research monitors and study sponsors, regulatory agencies, and regulatory and decision-making bodies will be informed of reportable adverse events (as described above) within 5 days of the event becoming known to the principal investigator.

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

18. **Statistical Considerations:** Describe the statistical analyses that support the study design.

The primary outcome will be total opiate use (as calculated by morphine-equivalents). This information will be obtained and calculated from the patient's medication administration record. Secondary outcomes t be studied include daily average pain score, using the visual analog system, following the cesarean delivery. A secondary analysis will take into account patients who received TAP blocks. This information is routine documented by the postpartum nurses and will be abstracted from the patient's chart. Pain scores for patients will the lidocaine patch will be compared to those who were randomized to receive the placebo patch. Data will be analyzed by intention to treat and comparisons between the groups will be made using student's t-test with adjustments made as needed for baseline demographic characteristics between the groups.

There is a notable dearth of literature on this topic. The only published data on lidocaine patches as pain control following c-sections are case reports. [1, 2] Expanding the literature search to include general surgery literature it has been shown that lidocaine patches improve post-operative pain following laparoscopic

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appendectomies.[3] Current literature investigating lidocaine patches after gynecologic surgery used expert opinion to determine that a difference of 2 in the VAS pain score would be clinically relevant. This lead to a power analysis determining a minimum of 16 patients per group would be required. Similarly, in general surgery literature when assessing lidocaine patches effect on postoperative pain after appendectomies a sample size of 40 was determined by expert opinion. Due to the dearth of information available, we are unable to calculate a predetermined sample size but feel with a goal of 50 patients in each arm we will be able to determine a clinically relative difference in VAS pain score of 2 or decrease in total postoperative opioid use by 20%.

1. Gilhooly, D., et al. (2011). "Topical lidocaine patch 5% for acute postoperative pain control." BMJ case reports(pagination).

2. Kim, J. B., et al. (2012). "Treatment for postoperative wound pain in gynecologic laparoscopic surgery: Topical lidocaine patches." Journal of Laparoendoscopic and Advanced Surgical Techniques 22(7): 668-673.

3. WooSurng Lee, KooYong Hahn, JungPil Hur, and YongHun Kim.Journal of Laparoendoscopic & Advanced Surgical Techniques.Sep 2018.1061-1067.http://doi.org/10.1089/lap.2018.0013

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SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.
Write here

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

B. DRUGS/BIOLOGICS ☐N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☒
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☒
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☒
4. The investigation will be conducted in compliance with the requirements for institutional (HIC)	☒

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	review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	
5.	The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Lidoderm 5% lidocaine patch was originally approved by the FDA for management of post-herpetic neuralgia. Lidocaine patches are commonly used in clinical practice for management of localized pain in surgical and non-surgical patients .

3. **Source:** Identify the source of the drug or biologic to be used. Hospital formulary

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a) Is the drug provided free of charge to subjects? ☐YES ☒NO
If yes, by whom? *Write here*

4. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

The lidocaine patches are already used in the hospital and do not require any special storage. They are currently stored in compliance with package insert guidelines in the hospital pharmacy. The cost of use is included in routine post-operative care for patients in the hospital.

Check applicable Investigational Drug Service utilized:

☐ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☒ None
☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation*.

5. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. Routine postpartum analgesia therapies include NSAIDs, acetaminophen, and opioids. These are all safe during the postpartum period.

b) State the maximum total length of time a participant may receive placebo while on the study.
The maximum time a participant may receive a placebo while on the study is 4 days.
c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
The greatest potential harm that may come to a participant as a result of receiving the placebo is less than optimal pain control.
d) Describe the procedures that are in place to safeguard participants receiving placebo.
The pain scores provided will ensure that adequate pain control is obtained for study participants since prn opioids will remain available to both participants receiving the placebo and those receiving the lidocaine patch.

6. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☒ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. Patients will be unblinded prior to hospital discharge and those on the lidocaine patch that noted the improvement will have the option to use the patch at home as SOC. If they patients found the effects of the lidocaine patch improved their pain scores and their subjective pain assessment then they could be written for a 7-day supply on discharge from the hospital with a discussion with their healthcare team. The coverage of the medication and cost to the patient after leaving the hospital would be dependent on their insurance status/type. Patients would need to request continuation of the lidocaine patch if desired.

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☐ NO If no, explain why this is acceptable. *Write here*

B. DEVICES ☒N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☐No

***If Yes, please be aware of the following requirements*:**

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
   Write here
3. **Source:**
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**

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a. Targeted for enrollment at Yale for this protocol: 100 total. 50 subjects in each arm (lidocaine patch versus no lidocaine patch)
b. If this is a multi-site study, give the total number of subjects targeted across all sites: n/a

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☒ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. **Recruitment Procedures:**

a. Describe how potential subjects will be identified. Potential subjects will be women with cesarean sections planned for surgery at Yale New Haven Hospital. We may include patient's that see private OBGYN providers in the community in the study since they have their surgeries performed at YNHH. Flyers will be provided for these locations
b. Describe how potential subjects are contacted. Subjects will be approached during their pre-operative counseling regarding the placement of lidocaine patches following completion of their surgery.
c. Who is recruiting potential subjects? The primary recruiters will Christopher Arkfeld, MD and Audrey Merriam, MD.

4. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☒Yes, some of the subjects.

☐No

If yes, describe the nature of this relationship.

PI and the study team could have seen potential patients during their well women visits, prenatal care, or if they had presented to the hospital in the ER or to be evaluated in OB triage for any obstetrical complaints during their pregnancy.

Prenatal care and postpartum care may be provided by one or both of the investigators but this is done as part of a team and the relationship with the patient will not be affected by their decision to participate or not participate in the study.

5. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

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☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: For patients that will call us to participate in the study and those that are our patients we will need to review the medical record to determine if potential subjects meet inclusion criteria or have exclusion criteria before participating in the study.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: For patients that will call us to participate in the study and those that are our patients we will need to review the medical record to determine if potential subjects meet inclusion criteria or have exclusion criteria before participating in the study.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   Subjects will be approached during their pre-operative evaluation or at the time of consent for cesarean delivery out of labor and will sign if willing to participate in the study. This may be on the same day of their c-section. They will be given adequate time to decide if they wish to participate and are able to decline the lidocaine patches at any time during the study. Patient typically present anywhere between 1-3 hours prior to c-section or the night before for pre-op testing during which there would be no time limit on reviewing the study.
7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   The same manner of determining whether or not a patient can consent for surgery will be used for participating in our study. If patients can demonstrate understanding of the situation, appreciation of the risks and benefits, and reasoning in their thought process, and can communicate their wishes then they would have capacity. Patients who received IV narcotic/anxiolytic medication within the preceding 60 minutes will not be asked to participate.
8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   Non-English speaking subjects will not be enrolled.

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As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☐
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☐

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

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For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☐ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☐
- Why would the research be impracticable to conduct without the waiver? *Write here*
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?
   Mother Name
   Mother MRN
   Delivery Date
   Gravida/Para
   Gestational Age
   Number of prior C-sections
   Surgical History
   TAP block yes or no
   MAR Record (amount of analgesic medication, including narcotics)
   Pain Scales

   T*he patients will be assigned a study participant number which will be used to organize the initial data collection.*

2. How will the research data be collected, recorded and stored? *The research data will be collected through medical record reviews and pre/post c section questionnaire and stored on secure computers.*

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server – Yale box ☒Laptop Computer ☐Desktop Computer ☒Other – redcap data collection

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? *Once the data has been collected the subjects will be deidentified for data analysis.*

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

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5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. *The data will remain on an encrypted in Redcap and secured laptop computer.*

6. If appropriate, has a Certificate of Confidentiality been obtained? *n/a*

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There may be no benefit to the patients during the post-operative period and pain may worsen because of use of placebo patch The benefit to society as a whole would be a potential decrease in opioid prescription amount and utilization after cesarean deliveries decreasing the amount of opioid prescriptions available to the community and likely decreasing the amount of unused opioids present in the community as well.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   The alternatives would be to adhere to our standard postoperative analgesic regiment of opioids, NSAIDs and acetaminophen. Occasionally, TAP (transversus abdominis plane) blocks are used at the discretion of the obstetric anesthesia providers for all patients that opt to enroll in the study and those that decline. The TAP blocks are performed once at the conclusion of the c-section.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   There will be no payments made to subjects.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   You or your insurance carrier will be expected to pay the costs of this treatment. Lidocaine patches are covered by most insurances as a part of obstetric care during admission to the hospital. All lidocaine patches prescribed at time of discharge will also be billed to your insurance.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? Yes the treatment will be available. *There is the potential for skin irritation due to the adhesive in the lidocaine patch.*
   b. Where and from whom may treatment be obtained? *Inpatient healthcare providers including residents, attendings, and nurses.*
   c. Are there any limits to the treatment being provided? *No.*
   d. Who will pay for this treatment? *It will be covered under traditional post-partum care and patient or patients insurance will have to pay.*

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e. How will the medical treatment be accessed by subjects? *Patient's will be able to seek out any treatments by asking their caregivers.*

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IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No ☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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