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

Protocol Title: Dexamethasone on Post-Operative Pain after C-section in Patients using Medication Assisted Treatment (MAT) during Pregnancy

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Version Date: 11/30/2022

(If applicable) Clinicaltrials.gov Registration #: **NCT04067609**

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.

SECTION I: RESEARCH PLAN

1. Statement of Purpose: State the scientific aim(s) of the study, or the hypotheses to be tested.
   Investigating if giving post-operative dexamethasone to patients with a history of opioid use disorder on medication assisted treatment during pregnancy improves their pain scores and decreases their opioid use after cesarean section.
2. Probable Duration of Project: State the expected duration of the project, including all follow-up and data analysis activities.
   5-5.5 years of data collection followed by six months of data analysis and patient follow up

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.

   In August 2018, the CDC published data from 1999 – 2014 showing that the US national prevalence rate of deliveries of women with opioid use disorder had increased from 1.5 to 6.5 per 1,000 deliveries.[1] Another recent study reported that 20-40% of pregnant women filled a prescription for opioids during their pregnancy[2], which does not account for opioids obtained illegally. Thus, rates are even higher if illegally obtained prescription opioid or heroin is considered. These are only a couple examples of data that have brought more attention to the effect of the national opioid crisis on the obstetrics in how opioid use among pregnant patients has risen dramatically.

   Complications are still incurred even if women are able to manage their opioid use during pregnancy as relapse risk and developing OUD is much greater during the postpartum period than antenatally, which carries with it risks of repeated cycles of withdrawal, contraction of infectious diseases, and even overdose and death.[3] For example, there were 211 maternal deaths in Colorado from 2004–2013 and 63 of them were by self-harm (accidental overdose or suicide). Most of these deaths occurred during the postpartum period and involved OUD (majorly opioid-related).[4] Additionally, another recent study discusses how overdose is the leading cause of maternal associated deaths in Utah from 2004-2013, (69 of 113) with opioids being the leading cause of drug overdose.[5] All of these deaths occurred in the postpartum period, which is thought to be due to increased stresses during delivery that carry into the postpartum period. Postpartum pain is one of these stresses, which is the area this study hopes to intervene on.

   One major intervention that is now the gold standard for use in pregnant women with opioid use disorder is medication assisted treatment (MAT), as its use is associated with improvement in fetal and obstetric outcomes, including compliance with prenatal care, lower rates of preterm birth, reduced fetal and neonatal morbidity and mortality, and a higher likelihood of newborn being discharged to his/her parents.[6]

   Medication assisted treatment includes regular (at least once a day) use of methadone, buprenorphine or suboxone. As a review: methadone is a synthetic opioid agonist that eliminates withdrawal symptoms and relieves drug cravings by acting on our brain's opioid receptors. It occupies and activates these opioid receptors more slowly than other opioids such as heroin, morphine, and opioid pain medication. In an opioid-dependent person, treatment doses do not produce euphoria. It is unique amongst MAT options in that it must be given daily by a methadone clinic. Buprenorphine is a partial opioid agonist, meaning that it binds to opioid receptors but activates them less strongly than full agonists. It also reduces cravings and withdrawal symptoms in

a person with an opioid use disorder without producing euphoria. This medication can be prescribed by a physician who is specially certified. Suboxone is a partial opioid agonist plus an opioid antagonist (naloxone), which was developed to further prevent medication misuse. It can also be prescribed by physicians who are specially certified.

It is well established that patients with opioid use disorder have difficulty with pain control, as chronic opioid exposure induces tolerance to the analgesic effects of opioids. Thus for our pregnant patients who undergo cesarean delivery, traditional postpartum pain strategies that include systemic or neuraxial opioids are less effective, and these women require a significantly larger amount of opioids post-partum. Specifically, studies have showed that MAT maintained women have similar analgesic needs and response during labor, but require larger amounts of opioids post cesarean section: 70% more in women maintained on methadone[7] and 50% more for women on Buprenorphine.[8] Further, undertreating pain is associated with worse maternal outcomes upon discharge including: persistent chronic pain, greater opioid use, delayed functional recovery, and increased postpartum depression, which are all factors associated with higher rates of relapse which can lead to overdose and death. [9]

Current guidelines in obstetrical anesthesia encourage non-opioid strategies and opioid-sparing treatment modalities to be used whenever possible in patients with a history of opioid use disorder, although the data for these strategies to treat postpartum pain comes from non-opioid using patients and we do not have data to help guide us in the opioid using population.[10] Recommended additional multimodal non-opioid strategies are currently non evidence-based in the MAT patient population are based on data extrapolated from post-operative pain studies in non-pregnant patients undergoing non-obstetric surgeries, and pain studies on pregnant patients without MAT use undergoing cesarean section. From this data, possible options for opioid-sparing strategies include Gabapentin, Clonidine, Magnesium, TAP block, Ketamine, and Dexamethasone.

For our study, we are most interested in an option that would be able to be administered consistently (same time/same way), that our own labor nurses could give, and without requiring the patient to have had an epidural placement. Further, Gabapentin, clonidine and ketamine are associated with CNS effects like sedation or confusion that could make health care providers less likely to be comfortable giving these women additional necessary narcotics due to possible worsened sedation or respiratory depression. Lastly, we wanted to give a drug that both obstetricians and pediatricians were comfortable with from extensive use in our maternal population. Thus, single administration IV dexamethasone was chosen for this study. Dexamethasone has been used as an adjunct for post-operative pain management in many types of surgeries. Although no large randomized trials exist, several small trials suggest an analgesic and opioid sparing effect of dexamethasone post-operatively for both pregnant and non-pregnant patients; however these studies excluded patients on MAT.[11-17]

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1. Haight, Sarah C., et al. "Opioid use disorder documented at delivery hospitalization—United States, 1999–2014." Morbidity and Mortality Weekly Report 67.31 (2018): 845.
2. Raymond, Britany L., Bradley T. Kook, and Michael G. Richardson. "The opioid epidemic and pregnancy: implications for anesthetic care." Current Opinion in Anesthesiology 31.3 (2018): 243-250.
3. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Committee Opinion No. 711: Opioid use and opioid use disorder in pregnancy. Obstet Gynecol 2017; 130:e81–e94.
4. Metz, Torri D., et al. "Maternal deaths from suicide and overdose in Colorado, 2004–2012." Obstetrics and gynecology 128.6 (2016): 1233.

5. Smid, Marcela C., et al. "Pregnancy-Associated Death in Utah: Contribution of Drug-Induced Deaths." Obstetrics & Gynecology 133.6 (2019): 1131-1140.
6. Meyer, Marjorie, et al. "Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy." European journal of pain 14.9 (2010): 939-943.
7. Reddy UM, Davis JM, Ren Z, Greene MF. Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes Workshop Invited Speakers. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes workshop invited speakers, opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. Obstet Gynecol 2017; 130:10–28.
8. Meyer, Marjorie, et al. "Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy." Obstetrics & Gynecology 110.2 (2007): 261-266.
9. Eisenach, James C., et al. "Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression." Pain 140.1 (2008): 87-94.
10. Soens, Mieke A., Jingui He, and Brian T. Bateman. "Anesthesia considerations and post-operative pain management in pregnant women with chronic opioid use." Seminars in perinatology. WB Saunders, 2019.
11. Mohtadi, Ahmadreza, et al. "The effect of single-dose administration of dexamethasone on postoperative pain in patients undergoing laparoscopic cholecystectomy." Anesthesiology and pain medicine 4.3 (2014).
12. Kjetil, Hval, et al. "The prolonged postoperative analgesic effect when dexamethasone is added to a nonsteroidal antiinflammatory drug (rofecoxib) before breast surgery." Anesthesia & Analgesia 105.2 (2007): 481-486.
13. Szucs, Szilard, et al. "Postoperative analgesic effect, of preoperatively administered dexamethasone, after operative fixation of fractured neck of femur: randomised, double blinded controlled study." BMC anesthesiology 16.1 (2015): 79.
14. Samona, Jason, et al. "Effect of intraoperative dexamethasone on pain scores and narcotic consumption in patients undergoing total knee arthroplasty." Orthopaedic surgery 9.1 (2017): 110-114.
15. Shahraki, Azar Danesh, et al. "The effect of intravenous Dexamethasone on post-cesarean section pain and vital signs: A double-blind randomized clinical trial." Journal of research in pharmacy practice 2.3 (2013): 99.
16. Maged, Ahmed M., et al. "Comparison of local and intra venous dexamethasone on post operative pain and recovery after caeseream section. A randomized controlled trial." Taiwanese Journal of Obstetrics and Gynecology 57.3 (2018): 346-350.
17. Cardoso, Monica MS, et al. "Effect of dexamethasone on prevention of postoperative nausea, vomiting and pain after caesarean section: a randomised, placebo-controlled, double-blind trial." European Journal of Anaesthesiology (EJA) 30.3 (2013): 102-105.

4. 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.

As there have been no studies on improving post-operative pain in this population (those with opioid use disorder on medication assisted treatment), we will perform a pilot study that is a double

blind, placebo controlled randomized control trial using 40 subjects with a history of opioid use disorder on medication assisted treatment during pregnancy. Similar to comparable studies that have shown an improvement in pain control postoperatively in the non-pregnant and/or non-MAT using population, we will use an online randomization tool to assign subjects to one of two groups in which subjects will receive a single administration of either 0.1 mg/kg of intravenous dexamethasone in 90mL of normal saline (experimental group) vs. 100mL of normal saline (placebo group) immediately upon the subjects' arrival to the PACU (post anesthesia care unit) after leaving the operating room from their scheduled or non-urgent c-section. We will then measure improvement in pain control by looking at pain scores via the standardly used and accepted Visual Analog Scale as well as quantities of opioid used post-partum prior to discharge from the hospital. We will look at patients' pain scores, as routinely collected by our post-partum nurses to determine necessary pain medication administration, and quantity of narcotic use (morphine equivalents) at 1-hour, hours, 12-hours, 24-hours, 48-hours, and 72-hours post operatively.
The dose chosen for our study (0.1mg/kg) was based on multiple other clinical trials for which this study designed was based on, including either pregnant patients undergoing c-sections or non-pregnant patients undergoing non-obstetric surgeries who were given perioperative dexamethasone. The following doses were used (eight referenced studies):

- Doses given for C-section studies: 8mg, 10mg, 16mg
- Doses given for non-c section operative studies: 0.1mg/kg in 3 studies (one with max up to 8mg), 16mg, 8mg

Our study will use weight-based dosing. This will help to prevent subjects from getting doses that are higher than the above listed studies for their body mass.

Participants will be asked at the time of consent if they agree to being contacted at 6 months and 12 months postpartum via phone call. The purpose of this phone call will be to follow up on continuation of their medication assistance therapy and inquire about any non-prescribed opioid use or illicit drug use. The purpose of this will be to assess if the adjuvant pain therapy of dexamethasone resulted in less opioid use and subsequent less risk of relapse in the postpartum period. We know from work by the Connecticut Maternal Morality Review Committee that over 1/3 of maternal deaths in Connecticut are related to substance abuse with the vast majority of these occurring in the remote postpartum period.[9] This will be a separate part of the consent form and participants will have the option to consent to the study alone but not the follow up portion.

1. Mohtadi, Ahmadreza, et al. "The effect of single-dose administration of dexamethasone on postoperative pain in patients undergoing laparoscopic cholecystectomy." Anesthesiology and pain medicine 4.3 (2014).
2. Kjetil, Hval, et al. "The prolonged postoperative analgesic effect when dexamethasone is added to a nonsteroidal antiinflammatory drug (rofecoxib) before breast surgery." Anesthesia & Analgesia 105.2 (2007): 481-486.
3. Szucs, Szilard, et al. "Postoperative analgesic effect, of preoperatively administered dexamethasone, after operative fixation of fractured neck of femur: randomised, double blinded controlled study." BMC anesthesiology 16.1 (2015): 79.
4. Samona, Jason, et al. "Effect of intraoperative dexamethasone on pain scores and narcotic consumption in patients undergoing total knee arthroplasty." Orthopaedic surgery 9.1 (2017): 110-114.

5. Shahraki, Azar Danesh, et al. "The effect of intravenous Dexamethasone on post-cesarean section pain and vital signs: A double-blind randomized clinical trial." Journal of research in pharmacy practice 2.3 (2013): 99.
6. Maged, Ahmed M., et al. "Comparison of local and intra venous dexamethasone on post operative pain and recovery after caeseream section. A randomized controlled trial." Taiwanese Journal of Obstetrics and Gynecology 57.3 (2018): 346-350.
7. Cardoso, Monica MS, et al. "Effect of dexamethasone on prevention of postoperative nausea, vomiting and pain after caesarean section: a randomised, placebo-controlled, double-blind trial." European Journal of Anaesthesiology (EJA) 30.3 (2013): 102-105.
8. Dube, Pratibha, et al. "Intravenous dexamethasone as an adjunct to improve labor analgesia: a randomized, double-blinded, placebo controlled clinical trial." Journal of clinical anesthesia 43 (2017): 6-10.
9. Maselli D, **Merriam A**, VanHouten C, McDowell T, Kostuic I. Pregnancy-Associated Deaths in Connecticut: Data from Connecticut Maternal Mortality Review Committee, 2015-2019. *Connecticut Department of Public Health* 2021.

5. 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

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.
   Subjects will include pregnant patients with a history of opioid use disorder who are compliant in their use medication assisted treatment (methadone, buprenorphine, suboxone) who are scheduled for cesarean delivery or who require a cesarean delivery during labor for non-urgent reasons, including

but not limited to arrest of dilation, arrest of descent, failed trial of labor, non-reassuring fetal heart tracing. As soon as individuals are identified as being eligible (in the clinic, at their pre-operative visit or on admission to the labor floor) they will be provided information on the study. Individuals will not be approached for consent unless they are scheduled for a cesarean delivery or require a non-urgent cesarean delivery out of labor (see inclusion criteria below)

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment 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	

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

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?
Inclusion:18 years or older, English-speaking, history of opioid use disorder with current use of MAT during pregnancy, scheduled for cesarean delivery for their current pregnancy for any indication [examples of **elective c-section** (decision made for c-section to be performed prior to onset of labor): fetal malpresentation, suspected macrosomia, prior c-section, abnormal placentation, patient preference], negative toxicology screen upon admission to the hospital for their cesarean section, no prior administration of betamethasone for fetal lung maturity within 24h of their scheduled cesarean delivery or women who require a c-section out of labor for non-urgent reasons and have received information about the study and the consent upon admission to the hospital and therefore have had adequate time to review the consent prior to the delivery ((Arrest of dilation, Arrest of descent, Failed induction of labor, Patient choice to discontinue trial of labor, Fetal malpresentation with no to minimal dilation (<4cm dilation), planned cesarean delivery at a later date presenting in labor or with rupture of membranes)

- Exclusion: under 18 years old, non-English speaking, screen positive for illicit substance(s) on their admission toxicology screen, require general anesthesia for their cesarean section due to maternal/fetal indication for non-anticipated urgency (thus no longer 'elective') or failure of adequate intra-operative pain control with spinal anesthesia, medical history including known cardiovascular disease, heart failure, uncontrolled hypertension (SBP ≥160mmHg and/or DBP ≥110mmHg), uncontrolled gestational or pregestational diabetes, active GI bleed or untreated peptic ulcer, untreated infectious diseases including tuberculosis or systemic candida, patients requiring a c-section out of labor for urgent reasons who have not received information about the study and the consent form upon admission to the hospital (Non-reassuring fetal heart rate tracing (persistent category II heart rate tracing), Category III fetal heart rate tracing, Acute placental abruption, Cord prolapse, Fetal malpresentation at advanced (>4cm dilation)).
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9. How will eligibility be determined, and by whom?
   Eligibility will be determined by review of the patient electronic medical chart by their obstetrics provider, who will be consenting them for the study, to assess their eligibility given their medical history as well as later determine exclusion laboratory criteria (admission toxicology screen)

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Risks with single administration dexamethasone are most relevant for special populations that have been excluded from this study, including:

Cardiovascular disease: Heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Use with caution following acute MI; corticosteroids have been associated with myocardial rupture.

Diabetes: may alter glucose production/regulation leading to hyperglycemia.

Gastrointestinal disease: (diverticulitis, recent intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess or other pyogenic infection) due to perforation risk

In regard to subjects who plan to breastfeed following delivery:

- Although the risk to newborns is unknown for any corticosteroid, use of dexamethasone is encouraged by ACOG (the ObGyn national body), and considered safe in pregnancy, especially for short term use. It is routinely given to mothers for fetal benefits, mainly lung maturity for suspected pre-term deliveries/neonates (ACOG Committee Opinion 713: Antenatal Corticosteroids for Fetal Maturity)
- When administered to lactating women, small amounts of corticosteroids entered human milk. Although data on the use of dexamethasone during lactation are not available, the American Academy of Pediatrics classified the corticosteroids prednisone and prednisolone as compatible with breastfeeding(Katz FH and Duncan BR: Entry of prednisone into human milk. N Engl J Med 293:1154, 1975. McKenzie SA et al.: Secretion of prednisone into breast milk. Arch Dis Child 50:894-6, 1975. Ost L et al.: Prednisolone excretion in human milk. J Pediatr 106:1008-11, 1985. Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human breast milk. Pediatrics 108:776-89, 2001.).
- If you plan to breastfeed your baby, this drug does appear in small quantities in breast milk and thus there is theoretical risk of use of corticosteroids have the potential to cause adverse events in a breastfeeding infant (eg, growth suppression, interfere with endogenous corticosteroid production) with chronic use, although information related to prolonged use is not available. Single doses of dexamethasone are considered compatible with breastfeeding; (WHO 2002).
- No data are available on the transfer of dexamethasone into human milk. It is likely similar to that of prednisone which is extremely low. Doses of prednisone as high as 120 mg fail to produce clinically relevant milk levels (equivalent of 18mg Dexamethasone). This product is commonly used in pediatrics for treating immune syndromes such as arthritis and, particularly, acute onset asthma or other bronchoconstrictive diseases. It is not likely that the amount in milk would produce clinical effect unless used in high doses over prolonged periods(Hale, Thomas W., and Hilary E. Rowe. *Medications and Mothers' Milk 2017*. Springer Publishing Company, 2016.).

- The half-life is 1 to 5 hours, with no drug at high enough levels to remain detectable in breast milk after one day.
- Breastfeeding while on corticosteroids carries minimal risk of exposure to the infant, which may be further decreased by nursing immediately before or more than 4 hours after the dose (Makol, Ashima, Kerry Wright, and Shreyasee Amin. "Rheumatoid Arthritis and Pregnancy." *Drugs* 71.15 (2011): 1973-1987 Ost L, Wettrell G, Bjorkhem I, et al. Prednisolone excretion in human milk. J Pediatr 1985 Jun; 106(6): 1008–11.).

Additional risk and reactions listed below are almost exclusively associated with repeated and/or high dose use and some are based on reports for other agents in this same pharmacologic class and may not be specifically reported for dexamethasone. (Frequency not defined):

Cardiovascular: Bradycardia, cardiac arrhythmia, cardiac failure, cardiomegaly, circulatory shock, edema, embolism (fat), hypertension, hypertrophic cardiomyopathy (premature infants), myocardial rupture (post-MI), syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Central nervous system: Depression, emotional lability, euphoria, headache, increased intracranial pressure, insomnia, malaise, myasthenia, neuritis, neuropathy, paresthesia, personality changes, pseudotumor cerebri (usually following discontinuation), psychic disorder, seizure, vertigo

Dermatologic: Acne vulgaris, allergic dermatitis, alopecia, atrophic striae, diaphoresis, ecchymoses, erythema, facial erythema, fragile skin, hyperpigmentation, hypertrichosis, hypopigmentation, perianal skin irritation (itching, burning, tingling; following IV injection), petechiae, skin atrophy, skin rash, subcutaneous atrophy, suppression of skin test reaction, urticaria, xeroderma

Endocrine & metabolic: Adrenal suppression, carbohydrate intolerance, Cushing syndrome, decreased glucose tolerance, decreased serum potassium, diabetes mellitus, fluid retention, glycosuria, growth suppression (children), hirsutism, HPA-axis suppression, hyperglycemia, hypokalemic alkalosis, menstrual disease, moon face, negative nitrogen balance, protein catabolism, redistribution of body fat, sodium retention, weight gain

Gastrointestinal: Abdominal distention, gastrointestinal hemorrhage, gastrointestinal perforation, hiccups, increased appetite, nausea, pancreatitis, peptic ulcer, pruritus ani (following IV injection), ulcerative esophagitis

Genitourinary: Defective (increased or decreased) spermatogenesis

Hematologic & oncologic: Kaposi sarcoma, petechial, tumor lysis syndrome

Hepatic: Hepatomegaly, increased serum transaminases

Hypersensitivity: Anaphylactoid reaction, anaphylaxis, angioedema, hypersensitivity

Infection: Infection, sterile abscess

Neuromuscular & skeletal: Amyotrophy, aseptic necrosis of bones (femoral and humoral heads), bone fractures, Charcot-like arthropathy, myasthenia, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), osteoporosis, rupture of tendon, steroid myopathy, vertebral compression fracture

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, subcapsular posterior cataract

Respiratory: Pulmonary edema

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

Populations at greatest risk with receipt of single dose IV dexamethasone will be excluded from the study.

12. 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 in pregnant women and fetuses (when no drug is taken), greater than minimal risk in non-pregnant subjects when taking drug
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? As only data collection from the medical record will be performed on the infants there is minimal risk to infants participating in the study

Greater Than Minimal Risk DSMP (subjects receiving study drug, Dexamethasone)

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator, the Institutional Review Board (IRB) or Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed greater than minimal for the following reasons: (choose those that apply)

1. **We do not view the risks associated with the investigational agent, Dexamethasone, as minimal risks.**
2. We do not view the risks associated with the combined use of _____and_____ as minimal risks.
3. Given the now established safety and validity of the current _____ in our prior work, we do not view the proposed studies as high risk.
4. Given our experience with the combined co-administration_____, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator, Victoria Wesevich and Audrey Merriam, according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND

2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. ***Please note*** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented**.** In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

□ **All Co-Investigators listed on the protocol.**
□ **Yale Cancer Center Data and Safety Monitoring Committee (DSMC)**
□ **Study Sponsor**

The principal investigator, Victoria Wesevich and advisor Audrey Merriam, will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

Please note: For any study that may be considered high risk, the IRB will be more focused on the safety requirements for the study and a DSMB will likely be required.

Minimal risk for infants and subjects receiving placebo

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [monthly]. 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, the Institutional Review Board (IRB) or Yale Cancer Center Data and Safety Monitoring Committee (DSMC) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects (receiving placebo and infants of all 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 via email as they are reviewed by the principal investigator. The protocol's research monitor: Yale Cancer Center Data and Safety Monitoring Committee (DSMC), will be informed of adverse maternal events within 5 days of the event becoming known to the principal investigator.

c. For multi-site studies for <u>which the Yale PI serves as the lead investigator</u>: n/a
   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

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

The primary outcome variable to be reported will be pain scores (via visual analog scale) during routine vital signs assessments by nursing throughout the standard postoperative hospital stay (2-4 days post-op) following cesarean section. Scores will be compared between women who received dexamethasone and those who received placebo using Student's t-test. Comparison of total morphine dose equivalents used by the patient during this period will be examined as a secondary outcome. The total morphine dose equivalents will be calculated from the total narcotic dose and appropriate conversion (i.e. dilaudid dose to morphine dose equivalents). This will be calculated as a total daily dose for the hospital stay and an average dose/d over the entire hospital stay. These 2 separate calculations will be used because it is presumed that narcotic use will decrease with each day post-op. Calculating an average dose/d over the entire hospital stay will account for women who are discharged on different postoperative days. This outcome will also be assessed using Student's t-test. Data will be assessed for normality prior to running the t-test in the primary and secondary outcomes and if there is not a normal distribution Wilcoxon Rank sum test. Demographic and baseline data will be analyzed using two sample t –test for continuous data and $\chi 2$ for categorical data to determine whether there are any differences between groups. All statistical tests will be two-tailed with the alpha level set at 0.05.

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): Dexamethasone

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: Dexamethasone	
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 Single use (rather than chronic or high-dose use) administration of dexamethasone in our select patient population (excluding patients at higher risk of adverse effects of the medication) at the standard dosage level does not involve a dosage level, route, or population that significantly increases the risk associated with the use of this drug. Please see additional text on breastfeeding information for safety in infants.	☒
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) 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.

Dexamethasone is a well-known and widely used long acting corticosteroid that is a strong anti-inflammatory agent. It has been used as an adjunct for post-operative pain management as well as improvement in perioperative nausea and vomiting in many types of surgeries. It decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

The majority of known risks with use of dexamethasone are associated with prolonged and/or high dose administration, especially in patients with specific medical co-morbidities, where as there are minimal risks with the single administration as we plan to utilize in our study in patients without the previously discussed co-morbidities. For example, an adverse reaction possible with our proposed dosing administration includes hyperglycemia, especially in those patients with uncontrolled diabetes. Please see previously discussed text on breastfeeding information for safety in infants.

3. Source: Identify the source of the drug or biologic to be used. The subjects would receive

a) Is the drug provided free of charge to subjects? ☒YES ☐NO

If yes, by whom? Funding obtained for this project will be used to cover the cost of the medication (vs. placebo) for the patient and will be obtained through a grant from Women's Health Research at Yale – Pilot Project Program.

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. This drug is consistently stored on the labor and delivery floor with appropriate storage, preparation, and stability techniques and information established by health care providers at the testing hospital facility, YNHH.

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.

There are no alternative therapies that have shown an established benefit in post-operative pain in this patient population.

b) State the maximum total length of time a participant may receive placebo while on the study.
The placebo-assigned subjects would receive a single administration immediately post-operatively

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
No foreseeable harm to participant (all patients undergoing cesarean section require consistent intravenous (IV) access and receive IV fluids post-operatively)

d) Describe the procedures that are in place to safeguard participants receiving placebo.
Not applicable

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. Write here

☒ NO If no, explain why this is acceptable. This is a single dose administration to evaluate potential for dexamethasone to improve pain scores and decrease narcotic use in the postoperative period. Based on this pilot study data there may be potential for continuation or multiple doses of this drug in future studies.

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:

a. Targeted for enrollment at Yale for this protocol: 40 participants (based on effect size predicted by comparable studies)

b. If this is a multi-site study, give the total number of subjects targeted across all sites: not applicable

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.

On a rolling basis, research team members will identify appropriate subjects (those with a history of opioid use disorder, currently on medication assisted treatment) at the time of their pre-operative prenatal visit for scheduled cesarean section

b. Describe how potential subjects are contacted.

Subjects' potential participation in this study will be addressed in-person at the time of their routine pre-operative, prenatal visit. They will not be contacted regarding this study by phone or email. On rare occasion, if a patient is failed to be identified or approached at this prenatal visit, the patient may be approached regarding participation in this study at the time of their pre-operative laboratory draw (at YNHH) the day prior to surgery or upon admission for their scheduled cesarean section.

Given that unscheduled cesarean sections may occur overnight when the primary investigators are not at the hospital, phone consent will be approached in these situations following the inclusion and exclusion criteria as described above. Additionally, these subjects will have been provided information about the study on their admission. Subjects will be identified by the primary care team and either Dr Wesevich or Dr Merriam will be notified of their potential eligibility. The investigator that was contacted will review the potential subject's chart for inclusion and exclusion criteria. Then, using mobile heartbeat phones the patient will be contacted and the research study explained to the patient over the phone. A member of the primary care team will be present to confirm the patient is correctly identified as the study is explained in more detail than the information they were previously provided. The patient will be given opportunity to ask questions and then the consent will be signed by the patient in front of a member of the primary team and the investigator will sign the consent within 24 hours.

Patients who require a cesarean delivery after a trial of labor will also be eligible for enrollment if the reason for cesarean delivery is non-urgent (see inclusion and exclusion criteria as described above). In these cases, the patient will have received information about the study and the consent form upon admission to the hospital.The primary team will contact Dr Wesevich or Dr Merriam about the potential participantand the investigator will have a conversation over the phone with the patient asking if they have any final questions and if they consent to participation. . The phone consent will occur as described above. Patients in these circumstances have adequate time to consider the study and consent if desired as their case is non-emergent and they received information about the study and the consent form on admission to the hospital. Subjects who do not receive information on the study and the consent form on admission will not be approached.

c. Who is recruiting potential subjects?
Research team members, including providers with obstetrical privileges at YNHH.

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.
The subjects recruited for this study will be patients under the care of obstetrics providers at YNHH. A research team member will participate in the patient's care during their delivery hospitalization at the time the study will take place

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

☐ 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: Write here

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: Write here

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' consent for participation in this study will be addressed in-person at the time of their routine pre-operative, prenatal visit. They will not be contacted regarding consent for this study by phone or email. On rare occasion, if a patient is failed to be consented at this prenatal visit, the patient may complete their consent process for participation in this study at the time of their pre-operative laboratory draw (at YNHH) the day prior to surgery or upon admission for their scheduled cesarean section.

Given that unscheduled cesarean sections may occur overnight when the primary investigators are not at the hospital, phone consent will be approached in these situations following the inclusion and exclusion criteria as described above. Additionally, these subjects will have been provided information about the study on their admission. Subjects will be identified by the primary care team and either Dr Wesevich or Dr Merriam will be notified of their potential eligibility. The investigator that was contacted will review the potential subject's chart for inclusion and exclusion criteria. Then, using mobile heartbeat phones the patient will be contacted and the research study explained to the patient over the phone in more detail than the information they were previously provided. Patients who require a cesarean delivery after a trial of labor will also be eligible for enrollment if the reason for cesarean delivery is non-urgent (see inclusion and exclusion criteria as described above). In these cases, the patient will have received information about the study and the consent form upon admission to the hospital. The primary team will contact Dr Wesevich or Dr Merriam about the potential participant and the investigator will have a conversation over the phone with the patient asking if they have any final questions and if they consent to participation. . The phone consent will occur as described above. Patients in these circumstances have adequate time to consider the study and consent if desired as their case is non-emergent and they received

information about the study and the consent form on admission to the hospital. Subjects who do not receive information on the study and the consent form on admission will not be approached. Participants will have the option to consent to the entire study, the randomized drug administration and follow up, or just the randomized study drug administration without follow up.

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.

These subjects will be consented at the time they are consented for their scheduled cesarean section. Thus, if the obstetrical provider deems the patient can provide informed consent for their cesarean delivery, that provider will also assess the potential subject's ability and capacity to consent to participation in the research participation in a similar manor.

Additionally, for unscheduled cesarean sections may occur overnight when the primary investigators are not at the hospital, phone consent will be approached in these situations following the inclusion and exclusion criteria as described above. Additionally, these subjects will have been provided information about the study on their admission. Subjects will be identified by the primary care team and either Dr Wesevich or Dr Merriam will be notified of their potential eligibility. The investigator that was contacted will review the potential subject's chart for inclusion and exclusion criteria. Then, using mobile heartbeat phones the patient will be contacted and the research study explained to the patient over the phone in more detail than they were previously provided.

Patients who require a cesarean delivery after a trial of labor will also be eligible for enrollment if the reason for cesarean delivery is non-urgent (see above inclusion and exclusion criteria) The phone consent will occur as described above. Patients in these circumstances have adequate time to consider the study and consent if desired as their case is non-urgent and they will have received information about the study and the study consent on admission to the hospital. Subjects who do not receive information on the study and the study consent on admission will not be approached.

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 be excluded from the study.

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

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?
   We will look at additional variables within the subjects' protected health information including the patients': age, prior pregnancy and delivery history, BMI, admission toxicology screen pain medications given during delivery hospitalization, gestational age, singleton vs. multiple gestation, and neonatal weight at birth.

2. How will the research data be collected, recorded and stored?

   Patients' data within the Epic will be reviewed by only the researchers involved in this project. All data extracted from the electronic medical record will be stored with de-identified subject ID number-codes for later analysis.

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

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?

   Data extracted from the electronic medical records will be de-identified. Coding for participants will be a password-protected document that will stored on the Yale Box Drive, a secured server.

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

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 be permanently deleted from the researchers' laptops and Yale Box Drive upon completion of the project.

6. If appropriate, has a Certificate of Confidentiality been obtained? Not applicable

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.)
Subjects of this study may receive the benefit of improved pain and require a smaller amount of opioid pain medication following their cesarean section as a result of participation in this study. It is possible that this improvement in pain and decrease in opioid requirement may decrease the risk of the poor maternal outcome associated with untreated pain and stresses incurred on patients with a history of opioid use disorder including those that lead to increased rates of relapse and overdose.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   There are no established or evidence-based methods of improving post-cesarean pain in patients with a history of opioid use disorder currently using medication assisted treatment. All currently used adjunctive opioid sparing strategies are used inconsistently and are not proven to be helpful in this patient population.
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.
   The patients will not receive financial compensation for their participation in this project
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.
   No cost to participants as they will receive the dexamethasone or placebo free of charge and they are coming to the hospital for their
   c-section.
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?
        i. Yes
    b. Where and from whom may treatment be obtained?
        i. YNHH by the subject's obstetrics team
    c. Are there any limits to the treatment being provided?
        i. No
    d. Who will pay for this treatment?
        i. The patient
    e. How will the medical treatment be accessed by subjects?
        i. The patient will be assessed and treated as is routine during their hospital stay for their c-section

APPROVED BY THE YALE UNIVERSITY IRB 12/12/2022

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.