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

Protocol Title: Comparison of Transverse abdominis plane block with the use of liposomal bupivacaine or Depomedrol and dexamethasone for postoperative cesarean delivery analgesia a double-blinded randomized controlled trial

Principal Investigator: Antonio Gonzalez Fiol

Version Date: Version April 5, 2021

Clinicaltrials.gov Registration #: NCT04393207

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.

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

SECTION I: RESEARCH PLAN

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

   Hypothesis: The use of a Transverse abdominis block with dexamethasone and depomedrol will provide equivalent analgesia to our current liposomal bupivacaine alternative, This will decrease postoperative opioid consumption.

   Specific Aims:

   1) Assessment of total opioid consumption in a 48hr period.
   2) Comparison between the efficacy of block of transverse abdominis plane block with plan bupivacaine vs. bupivacaine + dexamethasone/methylprednisolone acetate vs. bupivacaine + liposomal bupivacaine
   3) Assessment of functional recovery measured in steps taken.
   4) *Use of validated questionnaires to measure recovery after cesarean delivery ObsQoR-11 and pain catastrophizing survey to compare the answers to self-assessed recovery.*

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

   The study is expected to take 24-month for enrollment and another 12 months for data analysis. Given our early difficulties recruiting patients we now expect to finish the study by the end of 2026.

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 current literature on whether the transverse abdominis plane (TAP) block significantly reduces post-caesarian section pain is scarce and inconclusive. The TAP block offers analgesia by blocking the sensory nerves of the anterior abdominal wall. The procedure is performed under ultrasound guidance. After identification of the 3 abdominal muscle layers (external oblique, internal oblique and transverse abdominis muscle), medication is injected in the neurofascial plane between the internal oblique and the tranversus abdominis muscle (triangle of Petit).[1] *Previous studies have demonstrated limited (<24 hour) effect of the block when compared to the use of intrathecal morphine (considered to be the "gold standard" for postoperative analgesia). In a study by McMarrow et al.*[2] *they compared 4 post-caesarian pain control combinations including TAP blocks with local anesthetic (Bupivacaine) or saline after a spinal anesthetic with or without intrathecal morphine. That is, 1) Spinal with morphine + TAP with LA; 2) Spinal with morphine + TAP with saline; 3) Spinal with saline + TAP with LA and 4) Spinal with saline + TAP with saline. At 6 h the Morphine consumption was slightly reduced in the patients who received both intrathecal morphine and TAP blocks with LA compared to patients who received spinal saline and TAP with saline. At 24 h the TAP block conferred no benefit in terms of opioid consumption.*

Similarly, the study by Lee et al. demonstrated better pain scores for the first 2 h in patients receiving both intrathecal morphine and a TAP block with ropivacaine. At 24 h there was no difference in the pain scores for patients that received both intrathecal morphine and TAP blocks.[2] *On the contrary, a more recent study utilizing liposomal bupivacaine (which is FDA approved) has been utilized for TAP blocks for post cesarean delivery analgesia, demonstrating opioid reductions for up to 72 h.*[3] *Liposomal bupivacaine is a novel, multivesicular*

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

formulation designed for rapid absorption, prolonged release of bupivacaine, and analgesia following a single intra-operative administration into the surgical wound or for TAP blocks. This data suggests that the main limitation for TAP blocks in previous studies was the local anesthetic utilized for the block. The study of Baker et al. suggests that the use of liposomal bupivacaine also improves the patient's ability to ambulate, measured by time to get out of bed after surgery. The downsize for the use of liposomal bupivacaine is its cost. The value of a 266 mg vial is somewhere around $300.00. There seem to be other adjuvants that may help achieve similar prolonged analgesic effects at a lower cost for the institution and patients. For instance, the use of dexamethasone and methylprednisolone acetate has been shown to increase the length of peripheral and neuraxial blocks.[4,5] Our current anesthesia practices encourage the use of multimodal analgesia that aim at enhanced recovery after surgery (ERAS).[6] The ERAS model aims to decrease immobility, pain and postoperative ileus.

References:

1. Lee, A. J. *et al.* Ultrasound-guided bilateral transversus abdominis plane blocks in conjunction with intrathecal morphine for postcesarean analgesia. *J Clin Anesth* **25**, 475 482 (2013).

2. McMorrow, R. C. N. *et al.* Comparison of transversus abdominis plane block vs spinal morphine for pain relief after Caesarean section. *Br J Anaesth* **106**, 706 712 (2011).

3. Baker, B. W. *et al.* Transversus abdominis plane block with liposomal bupivacaine for pain control after cesarean delivery: a retrospective chart review. *J Pain Res* **11**, 3109 3116 (2018).

4. Pehora C, Pearson AM, Kaushal A, Crawford MW, Johnston B. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Db Syst Rev 2017;11:CD011770.

5. Li J, Perese F, Rubin LE, Carlyle D. Effective Pain Management After Total Hip Arthroplasty in a Sickle Cell Patient Emphasizing Dexamethasone Sodium Phosphate/Methylprednisolone Acetate Administered via a Peripheral Nerve Blockade. Pract 2018;Publish Ahead of Print:NA;

6. Jacques, V. *et al.* [Enhanced recovery following uncomplicated elective caesarean section in France: a survey of national practice]. *Ann Françaises D'anesthésie Et De Réanimation* **32**, 142 148 (2013).

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.

This is a double blinded, randomized controlled trial. The study will be composed of 3 groups
Group 1- Transverse abdominus plain block with liposomal bupivacaine + bupivacaine (LB) – TAP LB
Group 2 – Transverse abdominus plain block with bupivacaine (BP) + dexamethasone and depomedrol (BP-D)
Group 3 – CG - Control group (TAP block with plain bupivacaine)

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

1. Patients will be asked to participate after meeting their anesthesia treatment team and giving verbal consent to receive spinal anesthesia for their cesarean delivery.
2. A computer-generated, single block randomization scheme will be used to allocate patients to one of the three groups (CG Vs TAP LB group or BP-D group).

3. In the OR, the participants will receive clinical care determined by their treating physicians. As standard of care, the participants will likely receive spinal anesthesia according to standard protocols. This treatment will not be affected in any way by the protocol. The study intervention begins after the baby is delivered and the c-section incision is sutured. Post operatively subjects will receive pain medication according to their treating doctors' assessments and order according to the standard treatment. The postoperative pain management is not affected in any way by the study protocol.

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

After wound closure a TAP block will be performed according to randomization process as described above.

4. *The LB TAP block group will receive bilateral ultrasound guided block utilizing 10 ml of liposomal bupivacaine* and 25 ml of 0.25% bupivacaine + 5 mL saline.*
5. *The BP-D and TAP group will both receive bilateral ultrasound guided block utilizing 25 ml of 0.25% bupivacaine + 5 mL saline in addition to 5 mg PF dexamethasone (0.5 ml) + 40 mg (1ml) of methylprednisolone acetate (Depomedrol).* ***(Research procedure)***
6. The control group will receive 25 ml of 0.25% bupivacaine + 5 mL saline.

****Of note, only 10 mg of bupivacaine are considered free or active in the liposomal bupivacaine formulation. In order to provide adequate analgesia, the 20 mL's of bupivacaine are necessary. In addition, the use of the bupivacaine helps spread the medication into deeper structures to provide better analgesia as the bupivacaine is slowly released from its DepoFoam formulation.***

* A study was conducted to determine the amount of bupivacaine excreted in breast milk following epidural anesthesia for Cesarean delivery.[4] The free bupivacaine released from the DepoFoam formulation in EXPAREL is structurally the same as bupivacaine HCl/Marcaine. As such, the excretion in breast milk and protein binding will be the same.[5]Also bupivacaine is poorly absorbed orally.[6] Ortega et al (1999) conducted a study to determine the milk/serum ratio of lidocaine, bupivacaine and the major metabolite of bupivacaine, PPX in woman who received either a lidocaine or bupivacaine(mean dose ± SD, 82±29 mg) epidural for a Cesarean section. The mean±SD age, weight and height of the subjects was 30.0±6.3, 72.6±14.5 kg, and 160.8±6.5 cm, respectively. The mean APGAR score at delivery was 9.6.[4] The ratio of milk/serum was calculated based on the areas under the curves serum and milk concentrations ($AUC_{0\text{-}12}$ $\mu g*mL^{-1}*h^{-1}$). Samples and APGAR scores were taken at 2, 6, and 12 hours following the epidural. The ratios for bupivacaine and PPX were 0.34±0.24 and 1.37±0.24, respectively.
APGAR scores were 10 at all time-points.[4]

PHARMACOKINETICS
A typical dose of EXPAREL in a Cesarean section is 266 mg/20 mL either as local infiltration or as a transversus abdominus plane (TAP) block. In a prospective, blind assessor, randomized trial by Werner, patients undergoing lower abdominal surgery received a bilateral TAP with EXPAREL 266 mg/ 20 mL expanded with 40 mL of normal saline. Under ultrasound guidance, 30 mL of EXPAREL was administered to each side. Pharmacokinetic data was collected from 3 patients. The highest serum level (C_{max}) was 423 ng/mL reached at 30 minutes (T_{max}).[7] When EXPAREL 266 mg/ 20 mL was used as a local infiltration in incisions □3 cm the C_{max} was 365 ng/mL.[8]

1. EXPAREL® (bupivacaine liposome) Injectable Suspension. [Prescribing Information]. Parsippany, NJ. Pacira Pharmaceuticals, Inc
2. Silva M & Halpern S. Epidural analgesia for labor: Current Techniques. Local & Regional Anesthesia. 2010; 3:143-53
3. Halpern SH, Breen TW, Campbell DC, et al. A multicenter, randomized, controlled trial comparing bupivacaine with ropivacaine for labor analgesia. Anesthesiology. 2003;98:1431–1435
4. Ortega D, Viviand X, Lorec A, et al. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. Acta Anaesthesiol Scand. 1999' 43:394-397
5. Data on file. 4952. Parsippany, NJ: Pacira Pharmaceuticals, Inc.; 06/18
6. Reece-Stretman S, Campos M, Kokajko L, and the Academy of Breastfeeding Medicine. ABM Clinical Protocol#15: Analgesia and anesthesia for the breastfeeding mother, revised 2017. Breastfeeding Medicine. 2017; 12(9):1-7.

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

7. Werner J. Liposome bupivacaine via infiltration into the transversus abdominis plane: interim result from a randomized, controlled, multicenter trial. Presented at: Annual Meeting of the American Society of Regional Anesthesia and Pain Medicine, April 3-6, 2015, Chicago, IL.
8. Hu D, Onel E, Singla N, Kramer WG, Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. Clin Drug Investig 2013; 33(2):109-115

** "DEPO-MEDROL is an anti-inflammatory glucocorticoid for intramuscular, intra-articular, soft tissue or intralesional injection. It is available as single-dose vials in two strengths: 40 mg/mL, 80 mg/mL. This medication has been FDA approved for soft tissue injection (TAP block).
Amounts of methylprednisolone in breastmilk are very low and no adverse reactions in breastfed infants have been reported, even with intravenous doses of 1 gram. With maternal intravenous doses of 1 gram, fully breastfed infants would receive doses less than their daily cortisol output, and much less than the therapeutic dose used in neonates.[1,2] Accumulation of the drug does not occur in breastmilk with consecutive daily doses of 1 gram. Avoiding breastfeeding during the infusion and for as little as 2 hours after a 1 gram intravenous dose markedly reduces infant exposure. Smaller oral doses and local injections, such as for tendinitis, require no special precautions. Of note, we will be using doses smaller than 1 g and the injections are going to be injected in a poorly vascular area (low reuptake of medicine)

1. Drago BB, Kimura D, Rovnaghi CR, et al. Double-blind, placebo-controlled pilot randomized trial of methylprednisolone infusion in pediatric acute respiratory distress syndrome. Pediatr Crit Care Med. 2015;16:e74–81. [PubMed]
2. Huang YY, Chen MJ, Chiu NT, et al. Adjunctive oral methylprednisolone in pediatric acute pyelonephritis alleviates renal scarring. Pediatrics. 2011;128:e496–504. [PubMed]

Newborn safety.

A woman with multiple sclerosis who was 5 months postpartum received 1 gram of methylprednisolone infused intravenously over 2 hours on 3 successive days. She provided milk samples at 0, 1, 2, 4, 8 and 12 hours after each dose. Breastmilk levels at 0 and 12 hours were not quantifiable (<0.06 mg/L). Peak levels occurred at 1 hour after the end of the infusion and averaged 5.3 mg/L (range 5.1 to 5.6 mg/L). By 4 hours, after the dose, milk levels averaged 1.1 mg/L (range 1.0 to 1.6 mg/L) and by 8 hours, milk levels averaged 0.27 mg/L (range 0.2 to 0.37 mg/L). The authors calculated that a fully breastfed infant would have received an average of 0.19 mg/kg daily (range 0.16 to 0.21 mg/kg daily) of methylprednisolone, which is less than the lowest recommended therapeutic dose for infants. Withholding nursing for 2 to 4 hours after a dose would reduce the dose substantially. **Please keep in mind that this is based on 1 gram IV. Our dose would not achieve those peak levels, and even at 1 gram with all the IV bioavailability the expression of the drug is less than the normal neonatal cortisol production.**

Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-.

Methylprednisolone. [Updated 2020 Aug 17

6. The CG will receive a bilateral ultrasound guided block utilizing 25 ml of 0.25% bupivacaine + 5mL saline.. The randomization and procedure will be handled by a co-investigator not involved in the evaluation or data collection at the stablished time points. Patients will be recruited from 7am-5pm

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

and for elective CD

7. *Patients will be asked to complete the ObsQoR-11 at 24, 48 and 72 h.*
8. *All questionnaires will be completed prior to discharge. If the subject scores more than 10 on the EDS, primary care providers will be notified for arranging appropriate referral and follow up.*

All patients in this study will be receiving the standard of care determined by their treating physician and anesthesia.

Blinding Procedures

The patient and the research team member performing follow-ups would be blinded to the randomized drug group. The research team member will only be provided with the case #, and he/she will not access the patient record.

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

6. 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*

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

Woman, aged 18-45 presenting for elective cesarean delivery

8. 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 ☒

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

1. Patients between the ages of 18 and 45 presenting for cesarean delivery
2. ASA-1, ASA-2, ASA-3
3. No allergy to morphine
4. No allergy to bupivacaine
5. Patients with BMI > 45 will be excluded
6. No history of anxiety

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

7. No recent or chronic opioid use

Exclusion criteria

1. Need for Magnesium sulfate therapy
2. Neonatal admission to neonatal intensive care unit
3. Need for additional surgery other than cesarean delivery +/- bilateral tubal ligation (e.g. hysterectomy, cystotomy)

10. How will **eligibility** be determined, and by whom? Write here
Eligibility of patient participants will be determined by the study investigators.

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

There are no known risks associated with wearing an Actigraph GT3-X device (fit-bit device) in this protocol. If anything, an allergic reaction to the band is possible, yet unlikely. Complications related to the TAP block are rare as this procedure will be performed by experienced personal and under ultrasound guidance. Risks of the procedure includes infection, bleeding and bowel injury. Again, all these are potential risks, all of which become negligible when the procedure is performed using ultrasound guidance. The patient's treating anesthesiologist will discuss all associated risks separate from the study.
Although unlikely, some risks associated with local anesthetics may include local anesthetic toxicity, nausea, vomiting, itching and allergic reaction (anaphylactoid reactions).

12. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
Patients who participate will be monitored for any untoward effects, although none are expected.

13. 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? **Greater than 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 available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
    i. Greater than Minimal risk

Data and Safety Monitoring Plans (DSMP) Templates

420 FR.1

Greater Than Minimal Risk DSMP

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

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

principal investigator (Antonio Gonzalez) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator and the IRB 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 Transverse abdominis (TAP) block as minimal risks.
2. Given the now established safety and validity of the current TAP block in our prior work, we do not view the proposed studies as high risk.
3. Given our experience with the use of TAP block with the co-administration of liposomal bupivacaine, we do not view the proposed studies as high risk.

*** We have been using the TAP blocks with liposomal bupivacaine for over 1 yr. We estimate that we have performed close to 1000 of these procedures for post cesarean delivery analgesic management, and we have not seen a single complication directly or indirectly related to the block or the liposomal bupivacaine. Besides, the TAP block is also commonly performed for laparoscopic cases in the main OR. We estimate that close to 3000/yr for the last 3ys have been performed in the main OR. We are not aware of any complication related to the use of this block. This block is performed with ultrasound (US) guidance; hence we are visualizing our needle at all times. In addition, we utilize a blunt tip needle (not sharp end). The use of US and a blunt tip needle makes for a very safe block. If we would have seen 1 complication over the last yr, the calculated risk for a complication during this block would be calculated to be 1/4000. This would make the risk of a complication way less than 1%. If we were to take in consideration 3 yrs of experience performing this block without any complication, the risks is even lower than the worst case scenario of 1 case per year complication considering only last year.**
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 (*Antonio Gonzalez Fiol*) 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:

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

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.

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

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):

X All Co-Investigators listed on the protocol.

☐ Yale Cancer Center Data and Safety Monitoring Committee (DSMC)

☐ National Institutes of Health

☐ Food and Drug Administration (Physician-Sponsored IND #_____)

☐ Medical Research Foundation (Grant_____)

X Other Data Safety Monitoring Board (DSMB) or Committee (DSMC)

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

The principal investigator (*Antonio Gonzalez Fiol*) 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.

d. For multi-site studies for which the Yale PI serves as the lead investigator: **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*

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

If we were to seek a reduction in opioid consumption reduction, we would need a total of 240 patients (80 per group). This sample justification is based in our in-house (historical data) that showed a mean ± SD of morphine equivalent opioid consumption of 27.7 ± 29.3 mg. Assuming these estimated values, a sample size of 72 patients per group will result in a statistical power of 80% to detect a 50% reduction in the opioid consumption in the study group, with a significance level (alpha) of 0.05 using a two-sided unequal variance t-test. To allow for a 10% loss to follow up or dropout, a total of 240 (80 per group is recommended). From previous studies we have reviewed, the use of plain bupivacaine (without adjuvants) group would result in similar consumption of opioids in the first 24-48 h. The main benefit of a TAP block with bupivacaine is perhaps reflected in a decrease in opioid consumption in the first 10 h. We hypothesize that liposomal bupivacaine and the dexamthesone + depomedrol should have similar decreased in opioid effects. Hence, the numbers initially calculated for power analysis could still be used as described above. We will perform an interim analysis when we complete 50 patients per group to reassess power.

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/

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

2. 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

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

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 ☐

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	☒
3. 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).	☒
4. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☒

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.

The transverse abdominis block with liposomal bupivacaine has been described as a postoperative pain alternative for abdominal wall reconstruction[1], and directly injected at the incision site after cesarean delivery[2]. In both instances a total dose of 266 mg (20 ml) of liposomal bupivacaine has been used. In the first study (not in parturient) the liposomal bupivacaine was injected with direct visualization at the transverse abdominis. The second study consisted of injections at the surgical site. Besides, there is an ongoing (clinical trial) study looking into the efficacy of TAP blocks versus incision infiltration.[3] Liposomal bupivacaine (LB, EXPAREL®; Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA) is a prolonged-release formulation of bupivacaine that is approved by the US Food and Drug Administration (FDA) for single-dose infiltration for postsurgical analgesia, including TAP block.

References:

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

1. Mojtaba Fayezizadeh et al., "Efficacy of Transversus Abdominis Plane Block with Liposomal Bupivacaine During Open Abdominal Wall Reconstruction.," *American Journal of Surgery* 212, no. 3 (September 2016): 399–405, doi:10.1016/j.amjsurg.2015.12.026.
2. Malavika Prabhu et al. Liposomal Bupivacaine Block at the Time of Cesarean Delivery to Decrease Postoperative Pain. Obstetrics and Gynecology 2018; 132: 70-8
3. Post Cesarean Section Analgesic Safety and Efficacy of EXPAREL (Liposomal Bupivacaine) Infiltration Locally Versus Transversus Abdominis plane Infiltration. NCT033775495

The use of dexamethasone has been documented in chochrane database reviews to help extend the efficacy of perineural blocks. More recently, the use of methylprednisolone acetate has been shown to be a safe an effective way to prolong neuraxial as well as perineural nerve blocks. It is reasonable to think that the extended-release formulation from methylprednisolone acetate may reflect that of liposomal bupivacaine. The latter, at a fraction of the cost of liposomal bupivacaine.

1. Pehora C, Pearson AM, Kaushal A, Crawford MW, Johnston B. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Db Syst Rev 2017;11:CD011770.

2. Li J, Perese F, Rubin LE, Carlyle D. Effective Pain Management After Total Hip Arthroplasty in a Sickle Cell Patient Emphasizing Dexamethasone Sodium Phosphate/Methylprednisolone Acetate Administered via a Peripheral Nerve Blockade. Pract 2018;Publish Ahead of Print

3. **Source:** Identify the source of the drug or biologic to be used.
Liposomal Bupivacaine is manufactured by Pacira Pharmaceutical, Inc., Parsippany, NJ, USA), but they are not participating in the study.

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

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 Exparel (liposomal bupivacaine), is normally stored in our refrigerator in the Labor and delivery floor. Dexamethasone and methylprednisolone acetate are normally stored in our pyxis. We mix these drugs in our work room. The drugs are mixed and prepared using aseptic methods immediately prior to TAP block.

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**

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

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.

All patients will still receive our standard of care that includes the use of intrathecal morphine, intravenous acetaminophen and ketorolac.

b) State the maximum total length of time a participant may receive placebo while on the study.

N/A

c) Describe the procedures that are in place to safeguard participants receiving placebo.

Patients that do not receive the block will be ordered brake-trough pain medication according to our current practice.

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. *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

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

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: 240 (80 per group)
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: *Write here*

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: All patients scheduled for cesarean delivery that meet inclusion criteria will be approached.

* **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. All patients scheduled for elective cesarean delivery that meet inclusion criteria will be approached.

b. Describe how potential subjects are contacted. They will be approached directly by anesthesiologist/investigators. Obstetricians were approached by email

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

and encouraged to mention the study to patients in their office. Besides, both nurses and obstetricians were instructed by email to avoid utilizing the name of the local anesthetics to be used and their duration. Essentially, they were asked to use the following – "you will receive a TAP block with the standard of care drugs utilized at our institution and they all last anywhere from 24 – 48 hours."

c. Who is recruiting potential subjects? Study investigators including obstetricians and nurses that are part of the research team. The addition of nursing and obstetricians will facilitate our ability to gain patients trust and understanding of the study.

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. *Write here*

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.

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

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.
   Patients will be approached by a member of the research time during the pre-operative evaluation that occurs the evening before the scheduled day of surgery. All our scheduled surgery patients come in the evening for preoperative screening and blood draw. The consent will be provided to the patient for review. A member of the study team will then review the consent in detail with her. The person obtaining consent will answer all questions to the participant's satisfaction.

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.

   Capacity to provide consent will be assessed by one of the investigators. If the patient is deemed not competent, they will not be included in the study

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.

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?

   Age, parity, gestational age, number of pregnancies, number of previous cesarean deliveries, height, weight, first opioid request, opioid consumption at 12, 24, 36 and 48 hrs, Pain Visual analogue score at rest and with movement assessed at 12, 24 36 and 48 hrs, level of sedation and side effects of medications (i.e Nausea, Vomiting and pruritus), use of medications to treat nausea and vomiting and/or pruritus. Number of steps every 6 h for a 72 h period.

   The newborn record of all participants will also be reviewed, collecting Apgar scores, and

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

general wellness, weight, feeding behavior and discharge information.

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

How will the research data be collected, recorded and stored? Study information will be collected and kept in research chart. Subjects will be given a number and all data will be entered into a secure online data base on a computer that is password protected and encrypted. The link will be maintained by the PI. How will the digital data be stored?
☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☐Secured Server

☒Laptop Computer ☒Desktop Computer ☐Other

2. 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? The participants research chart will be secured in a locked file cabinet in the PI's or coordinator's office. The electronic database will be password protected and encrypted.

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

3. 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. Data will be kept until the data is analyzed and published. Once this is complete the charts with the identified information and the link will be destroyed per Yale's policy.

4. 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.)
Given that liposomal bupivacaine and dexamethasone + depomedrol may last for 24-48 hrs secondary to its gradual drug release, the patients that are randomized to receive a TAP block in any of these two arms may benefit from better postoperative pain relief. For those patients randomized to the control group there may be no additional benefit, but they will receive our current standard of care.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   The only alternative is to not participate.

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 is no payment for participation.

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.
   The patients that are randomized to receive the liposomal bupivacaine or the dexamethasone and depomedrol will not be charged for the cost of the drug, as the drug is been provided by YNHH pharmacy. Yale NHH is

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

not charging for the drugs.

The patient that are randomized to the control group will be charged for the current standard of care at our institution.

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 patient will be referred to a specialist in the very unlikely event of a research-related injury.*
    b. Where and from whom may treatment be obtained? *See below*
    c. Are there any limits to the treatment being provided? *See below*
    d. Who will pay for this treatment? *See below*
    e. How will the medical treatment be accessed by subjects? *See below*

This research involves greater than minimal risk, but the actual risks of physical harm is calculated to be < 1% given the use of ultrasound guidance. In the rare event of physical or emotional harm. Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If patients are injured as a result of your participation in this study, treatment will be provided. Patients or their insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Patients do not give up any of their legal rights by signing this form

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024

IMPORTANT REMINDERS

Will this study have a billable service? **Yes** ☐ **No** X

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** X **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** X **No** ☐

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

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

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.**

APPROVED BY THE YALE UNIVERSITY IRB 1/29/2024