March 17, 2021

NCT03977454

Periarticular Injection Versus Peripheral Nerve Block in Total Hip Arthroplasty

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

Protocol Title: Periarticular injection versus peripheral nerve block in total hip arthroplasty: a single center randomized controlled trail (RCT) study

Principal Investigator: Jinlei Li, M.D., PhD.

Version Date: Version 8, March 17, 2021

(*If applicable*) Clinicaltrials.gov Registration #: NCT03977454

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.
   Preoperative quadratus lumborum block (QLB)/lateral femoral cutaneous nerve block (LFCNB) with ropivacaine and glucocorticoids provide more effective analgesia than periarticular injection (PAI) with the same mixture in total hip arthroplasty (THA).

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   We anticipate that the enrollment will require 2 years to complete and another year for completion of data collection, final analysis and publication. Therefore, we project the duration of the project to be 3 years.

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.

   Strategies to improve perioperative analgesia of THA patients are clearly needed. Decreasing perioperative pain improves patient satisfaction, timing and ability of physical therapy, hospital length of stay, as well as long term functional recovery.

   Debate surrounds the issue of whether peripheral nerve blockade or PAI should be employed within a contemporary, comprehensive multimodal analgesia pathway for total hip arthroplasty [1,2]. Most studies showed that peripheral nerve block and Liposomal bupivacaine PAI provide equal or better analgesia than plain bupivacaine PAI, but the comparison between peripheral nerve block and Liposomal bupivacaine is unclear [3].

   The most common type of PAI is with plain bupivacaine or with Liposomal bupivacaine. Traditional peripheral nerve block utilized in THA includes femoral nerve block, facsica iliaca block and lumbar plexus block, in the format of single injection or continuous catheter placement.

   There are limitations in traditional nerve blocks. Practitioners are concerned about the many disadvantages/inconvenience of a continuous nerve catheter, yet a single injection nerve block does not last longer than 15-24 hours. There are also inherent issues with earlier peripheral nerve block techniques such as motor weakness and delay in physical therapy, some even advocated to move away from nerve block and transition toward PAI [1,4].

   Fortunately, in recent years emerging/newer peripheral nerve block techniques such as ultrasound guided quadratus lumborum block (T5-L1) and lateral femoral cutaneous nerve block (L2-3), have shown promising results in THA by offering better analgesia without the motor weakness seen in traditional peripheral nerve block techniques such as femoral nerve block or lumbar plexus block [1,2]. An RCT, could be the first one, is undergoing in University of Alabama , by comparing QLB block with control (systematic analgesics), listed on https://clinicaltrials.gov/ct2/show/ NCT03977454.

   At Yale New Haven Hospital, we have had successful experience of using the newer and motor-sparing blocks in conjunction with local anesthetic adjuvant glucocorticoids (please see below) to make THA, a 24-48 hour-stay procedure, an outpatient same day surgery. Our pilot study (see table

on page 8) showed the average perioperative opioid consumption was 24.5 (14.0) vs 11.9 (6.0) milligram morphine equivalent in PAI group vs nerve block group respectively.

As of now, there are no studies comparing single injection motor-sparing nerve blocks such as QLB/LFCNB with glucocorticoids vs PAI in THA.

Relevance of short and long acting glucocorticoid in perioperative analgesia:
The usage of glucocorticoids to augment nerve block's effects derived from local anesthetics alone such as ropivacaine, bupivacaine, have been shown to be safe and effective in many contexts. [3] [4] [5] [6] Ropivacaine is newer long acting local anesthetics. It has a couple of advantages over bupivacaine, for one, it has selective blockade effect in the sense that it can provide patients with comparable sensory blockage effect and analgesia yet with much less motor blockade effect as compared to bupivacaine. In lower extremity procedures ropivacaine is better with less risk of weakness and fall. In addition, ropivacaine has less risk for severe cardiac toxicity in the event of local anesthetic systemic toxicity.

Long acting glucocorticoids have been used for various chronic pain procedures [7], including back pain control through epidural anesthesia [4], facet joint injection, and selective nerve root injection [8-11]. Lately its use has been extended to persistent post-surgical pain treatment through paravertebral nerve blockade [9]. Long acting glucocorticoids have demonstrated efficacy for long-term, post-surgical, pain control yet its role in the immediate perioperative setting is largely unknown. Of note, Long acting glucocorticoids, such as methylprednisolone acetate (MPA) and betamethasone acetate, are not commonly used for acute pain control, and this in part is due to the variable onset time [12]. For example, when 80 mg MPA was administered intrathecally, the peak onset time was 1 day, lasting up to 21 days. [13,14] Therefore as a stand-alone agent, it may be ideal for prolonged pain control, but may not consistently offer reliable acute pain control.[15,16] Instead, MPA serves as the reservoir and confers the sustained- and extended-release characteristics [12].

A water-soluble glucocorticoid, such as dexamethasone sodium phosphate (DEX), with instant onset and prolonging blocks for 6-8 hours, can bridge the effects between local anesthetics and long acting glucocorticoids.

In summary, currently available long acting local anesthetics such ropivacaine and bupivacaine have duration of action of about 15-18 hours, which is not sufficient for a major surgery such as THA. Glucocorticoid have been shown to prolong the duration of nerve block by 6-8 hours (DEX) and by days (MPA). The onset of MPA needs 24 hours, therefore we use both DEX and MPA to maximize regional anesthesia' effect on opioid-sparing and motor-sparing pain control and provide patients with patient control for about 48 hours or longer.

We therefore use Dexamethasone sodium phosphate/methylpredisone acetate (DEX/MPA) for nerve blocks in total hip arthroplasty. DEX [17,18] and MPA [19] are FDA approved for intramuscular, intra-articular and soft tissue administration, and have been safely and effectively used in nerve blocks. It has been shown to produce both rapid onset and prolonged duration of effects. [17,18] . In addition, the types of nerve block we perform are not into the neuronal tissues, rather are around

the muscles and within soft tissues. For example, QLB is performed between quadratus lumborum muscle and psoas muscle, and LFCNB are perform between Fascia Lata and Fascia Iliac.

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.

To support our hypothesis that preoperative quadratus lumborum block (QLB)/lateral femoral cutaneous nerve block (LFCNB) provides more effective analgesia than periarticular injection (PAI) in total hip arthroplasty (THA), we will look at the following outcomes:

Primary outcome: Daily opioid consumption during the hospitalization
Secondary outcomes:

[1]. Pain intensity and physical functioning daily while in hospital: using a Brief Pain Inventory (Copyright 1991 Charles S. Cleeland, PhD, Pain Research Group), see attached; pain intensity, satisfaction and caregiver experience at 2 weeks by phone call to be collected by researchers;
[2]. From chart review: time to first physical therapy session, physical therapy note with Boston University activity measure for post-acute care (AM-PAC) basic mobility scores, occupational therapy note with AM-OAC daily activity scores;
[3]. Safety data: WBC, serum glucose and any complications;
[4]. Length of hospital stays;
[5]. Hip range of motion (ROM) scores at 6-weeks postop in surgeon office using Harris Hip Score;
[6] Post discharge **O**pioid consumption, pain control, functional and surgical outcomes relative to work/life baseline will be obtained via chart review up to 6 months post-op.

Since both QLB/LFCNB nerve block and PAI techniques are both routinely used as standard of care anesthesia for THA, the study intervention will be the randomization to assign patients to one of these treatment options and assess their response from post-op patient questionnaires and data collection.

Patients who are scheduled for elective unilateral primary total hip arthroplasty will be introduced to the study before the surgery when they visit the hospital for pre-op evaluations. An information booklet will be handed out at the surgeon's office during pre-operative visits and also in our anesthesia Pre-Admission Testing (PAT) clinic. A study team member will be present to meet with the patients and answer any questions they may have at the PAT visit. Subjects may sign consent at that time or may also be able to sign the study consent on the day of their surgery, prior to any study activities or anesthesia commencing.

The randomization will be done by the departmental statistician prior to the surgery for each patient. The randomization code and scheme will be generated through a computer-generated process using a blocked randomization schedule in variable blocks of 4 and 5 to avoid selection bias. Subject identification numbers (SIN) will be randomly pre-assigned to study participants and

the corresponding intervention model will be stored and assigned from our web-based system to assure concealment of intervention allocation. Individuals complying with all inclusion and exclusion criteria and consenting to study participation will be randomized to one of the two following study groups in a 1:1 ratio as outlined below:

Group 1: Nerve blocks (QLB/LFCNB) to be placed preoperatively with DEX/MPA, per standard of care of anesthesia block service.

1. QLB: 40ml 0.2% ropivacaine with 5 mg DEX/ 40 mg MPA; and
2. LFCNB: 20ml 0.2% ropivacaine with 5 mg DEX/ 40 mg MPA

Preoperatively, Group 1 patients will receive nerve block per standard of care as stated above. Intraoperatively, Group 1 will NOT receive PAI.

Group 2: Intraoperatively, the surgeon will perform PAI with exactly the same medication as group 1, ie, 60 ml 0.2% ropivacaine and 10 mg DEX/ 80 mg MPA, per standard of care of Surgeon. Group 2 will NOT receive any nerve blocks.

Study participants who return for contralateral THA, that have previously been randomized, will be offered participation in an open-label crossover arm with assignment to the alternative study group. This open-label phase will be only observational and study visits and data collection will be the same as for the randomized arms. If the participant declines assignment to the alternative study group, they will be asked permission to continue the same study follow up procedures and data collection. If participant declines remaining in the observational study, no data will be recorded.

Both groups:

Intraoperatively all subjects will receive spinal anesthesia with 0.5% bupivacaine 2-3 ml (10-15 mg) for surgical anesthesia under standard ASA monitors and sedation as needed (intravenous Midazolam, and/or Fentanyl, and/or Propofol).

In the Post Anesthesia Care Unit (PACU) pain control will be managed by intravenous morphine, ketoralac or oxycodone before or after subjects can tolerate oral intake respectively. After discharge from PACU to orthopedic floor, they will receive standardized pain management. Specifically, **all** subjects will receive scheduled 975 mg acetaminophen Q6 hours and Celebrex 100 mg Bid as standard of care pain management. Oral opioids will be oxycodone 5mg/10mg/15 mg Q4 hrs PRN for mild/moderate/severe pain respectively, per standard of care at YNHH. Intravenous morphine 2mg/4mg/8 mg Q 3hrs is also available for breakthrough pain, per standard of care at YNHH.

When it is time to discharge patients to home or rehabilitation, all subjects will be instructed to continue with 975 mg acetaminophen Q6 hours for 14 days. Discharge opioids prescriptions include oxycodone 5 mg (50 pills in total) with the dosing of 1-2 tabs Q4hrs PRN.

We will follow-up with subjects daily while they are in the hospital and the BPI questionnaire will be completed daily while hospitalized.

Patient's will receive a phone call for their 2-week follow up visit and a medical record review will be completed to obtain the information. At this visit, the patient satisfaction and caregiver experience questionnaire, functional assessment utilizing PT and OT notes in the chart; BPI and results will be completed. Additionally, we will inquire about the amount of opioid medication they have used.

Chart review will be performed up to 6 months post-operatively to collect the following information: ROM and Harris Hip Scores obtained at 6-weeks post-op in surgeon's office; opioid consumption; pain control; functional and surgical outcomes relative to work/life baseline.

Please see ICF addendum for subjects previously enrolled returning for surgery on the contralateral hip.

All medications used in this protocol are considered standard of care at this institute.

5. Genetic Testing N/A ☒

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.
   Adult, English speaking patients who are scheduled for elective unilateral primary total hip arthroplasty are the population we will recruit for this study.

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. None

☐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 Criteria:
   [1]. Elective unilateral primary THA;
   [2]. All surgical approaches
   [3]. ASA status I, II and III.

   Exclusion Criteria:
   [1]. Patient refusal;
   [2]. Age less than 18 years

[3]. Those with cognitive dysfunction, psychiatric disorder, or non-English speaking patients that cannot consent or communicate clear understanding of the protocol with research team;
[4]. Coagulopathy;
[5]. Allergy to local anesthetic bupivacaine, ropivacaine, or DEX/MPA;
[6]. Uncontrolled diabetes defined as taking insulin, day of surgery finger stick glucose > 300 mg/dl, or HbA1C > 7.5%;
[7]. Block site or systemic infection;
[8]. Immune compromise (e.g., HIV, chronic glucocorticoid use);
[9]. Chronic pain being treated with any opioids, gabapentin or pregabalin prior to surgery.
[10]. Women of childbearing potential who are determined to be pregnant through routine pre-operative testing will not be eligible.

9. How will **eligibility** be determined, and by whom? Write here
   Eligibility will be determined by study team members, Co-Investigators, and/or the Principal Investigator.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
    Since the study intervention includes randomization to either standard of care analgesia plan, which are both acceptable treatment methods, the risks involved with participation are minimal. They include a possible risk of privacy, which we will attempt to minimalize by assigning each subject a unique study code number and not use personal identifiers such as their name for case identification.

    The tools we will use for data collection about their pain management, functional status, and surgical outcome are validated tools which will be administered by trained study personal familiar with patient care. They will be able to recognize when a subject may be too tired, or uncomfortable to answer questions and will defer to another time when the patient will be more able to answer the questions. All patient evaluations will be done with the utmost respect for the subject's comfort and privacy.

    Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
    Risk of privacy and confidentially will be minimalized by assigning a unique study code number to each subject to avoid disclosure of their personal identity, trained study personal will be respective of subject's level of comfort during any in-person interviews and will reschedule if necessary, and follow up data will be extracted from the medical record directly without any inconvenience to the subject once they have been discharged from the hospital.

11. **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 – see Data and Safety Monitoring Plan below:

1. Personnel responsible for the safety review and its frequency:
The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which shall be every 6 months for this study. 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 the Yale Medical School Department of Anesthesia 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 reason:

- We do not view the risks associated with the randomization of subjects to one of two treatment arms as minimal risk.

- Given our experience with the combined co-administration of periarticular injections and peripheral nerve blocks as standard of care, 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, Jinlei Li, 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*. Adverse events will be 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 will 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 may be submitted.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's Data and Safety Monitoring Board (DSMB) sponsoring department of Anesthesiology, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:

□ All Co-Investigators listed on the protocol.
□ Medical Monitor
□ IRB

The principal investigator Jinlei Li, M.D., PhD. will conduct a review of all adverse events upon completion of every study subject. Any adverse event deemed serious or unexpected, will be reviewed by the Medical Monitor, Dr. Arsenio Bustos. Based on the Medical Monitor's determination, 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.

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

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- see plan above 11a.

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

12. **Statistical Considerations:** Describe the statistical analyses that support the study design. Methods of analysis, including statistical techniques:

Baseline comparability: It is expected that the randomization process will produce reasonably comparable groups. Descriptive statistics mean (standard deviation), median (interquartile range), and frequencies will be used to characterize demographic, clinical, and other baseline variables of the study participants. Student t-test, Wilcoxon rank sum test, and Chi-square test will be used for statistical comparisons as appropriate.

Interim monitoring: Interim monitoring will focus on recruitment, adherence to protocol, baseline comparability of treatment groups, completeness of data retrieval, and uptake of the assigned intervention. A set of monitoring tables will be generated by YCAS for this purpose. No interim looks for efficacy are planned.

Sample size/statistical power considerations:
The primary hypothesis is that peripheral nerve block will lead to significantly less total opioid consumption compared to Periarticular injection. From our 'in-house' historical data of mixed patients with Liposomal bupivacaine PAI and block procedure, the pooled standard deviation (SD) of total opioid consumption in 24 hours was estimated to be 13 MME. Assuming the same SD and a significance level (alpha) of 0.050, group sample sizes of 75 and75 achieve 80.3% power to detect a two-group difference of 6 MME in total daily opioid consumption (Cohen's effect size = 6/13=0.46) using a two-sided two-sample unequal-variance t-test. To allow for up to 20% loss to follow-up or attrition rate, we will enroll a total of 190 subjects (95 per group) for this planned study.

Statistical analyses: Data analyses will be conducted in collaboration with Dr. Feng Dai from the Yale Center for Analytic Sciences and will be performed with the use of SAS v9.4 (SAS Institute, Cary, NC). Quantitative analyses will include basic descriptive measures of central tendency (Mean, SD, median, interquartile range, frequency) for all measures (demographics, baseline characteristics, outcomes, etc.) collected pre-and post-surgery.
The extent and distribution of missing data will also be examined for all baseline variables. As it is generally not recommended to report the significance of comparing baseline characteristics in clinical trials, we will only list the summary statistics per treatment group and in total group in a table when we present results for publications.

The primary outcome (opioid consumption) will be analyzed in a modified intent-to-treat (ITT) analysis, in which a participant needs to have at least one observed outcome after randomization. Treatment effect will be determined as the difference in the opioid consumption between two groups at 24 hours (our primary endpoint), with a two-sided p-value of less than 5% used to test for statistical significance. To model the trend of the repeatedly measured opioid outcome over time, a linear mixed-effects regression model (MRM) will be fit with an unstructured covariance matrix specified to account for the

within-subject correlation of repeated measures. Fixed effects for treatment (DEX+MPA vs. DEX), time (e.g., hours, days), and time-by-treatment interaction will be estimated, presented as least square means and their corresponding 95% confidence intervals (CIs). The robust standard errors and test

statistics involving the fixed effects will be computed by invoking the EMPIRICAL option within the SAS Proc Mixed procedure. Comparisons of least squares means between treatment groups at each time point, or between time points within a treatment group will be performed.

The statistical comparisons of two groups on continuous secondary outcomes measured only at once (such as length of stay, duration of block) will be performed by two-sample t-test or Wilcoxon rank sum test as appropriate. Like the opioid consumption, the repeatedly measured pain scores will also be analyzed all together by the MRM analysis. The method provides valid results under the assumption that missing data is missing at random, gaining power and resulting in unbiased estimation than two-sample test of complete cases at each single time points. For categorical outcomes (e.g., adverse events) we will use Chi-square or Fisher's exact test for comparison.

Our analyses will not be adjusted for multiple comparisons. The interpretation of our primary outcome is not affected but any findings related to our secondary outcomes should be interpreted with caution unless the p-values for them are highly statistically significant (i.e., $p < 0.001$).

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

B. DRUGS/BIOLOGICS ☐N/A

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

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

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.

We are using 2 standard of care approaches with FDA medications in THA at YNHH. Dexamethasone sodium phosphate/methylpredisone acetate (DEX/MPA) for nerve blocks in total hip arthroplasty. DEX [17,18] and MPA [19] are FDA approved for intramuscular, intra-articular and soft tissue administration, and have been safely and effectively used in nerve blocks. It has been shown to produce both rapid onset and prolonged duration of effects. [17,18]. There is no additional risk associated with these medications as these approaches are part of the standard management for patients having THA.
SEE ALSO BACKGROUND INFORMATION PAGE 2

Group 1: Nerve blocks (QLB/LFCNB) to be placed preoperatively with DEX/MPA, per standard of care of anesthesia block service.

1. QLB: 40ml 0.2% ropivacaine with 5 mg DEX/ 40 mg MPA; and
2. LFCNB: 20ml 0.2% ropivacaine with 5 mg DEX/ 40 mg MPA Preoperatively, Group 1 patients will receive nerve block per standard of care as stated above.Intraoperatively, Group 1 will NOT receive PAI.

Group 2: Intraoperatively, the surgeon will perform PAI with exactly the same medication as group 1, ie, 60 ml 0.2% ropivacaine and 10 mg DEX/ 80 mg MPA, per standard of care of Surgeon. Group 2 will NOT receive any nerve blocks.

3. Source: Identify the source of the drug or biologic to be used. YNHH
Medications are identified with doses in section 2

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

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

Check applicable Investigational Drug Service utilized:

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

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

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?

C. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: 190 in total There will be 95 in each of the two groups.
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

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

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

* 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. 190

b. Describe how potential subjects are contacted.

Patients who are scheduled for elective unilateral primary total hip arthroplasty will be introduced to the study before the surgery when they visit the hospital for pre-op evaluations. Patients will be identified through review of operating room scheduling and Pre-Admission Testing appointments scheduled to coincide with the date of the planned surgery. Patients may be recruited through 2 ways. Pt will be introduced to this study before the surgery when they visit the hospital to meet health care works including our block team member. An information booklet will also be handed out at the surgeon's office during pre-operative visits, in which case they may contact the study team directly, and also in our anesthesia Pre-Admission Testing (PAT) clinic. A study team member will be present to meet with the patient s and answer any questions they may have at the PAT visit. Subjects may sign consent at that time or may also be able to sign the study consent on the day of their surgery, prior to any study activities or anesthesia commencing. It is on the day of surgery that patients will sign the consent.

c. Who is recruiting potential subjects? The Principal Investigator, Clinical Research Nurses, Co-Investigators, and Research Assistants as listed with this protocol.

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. It is possible that some of the subjects may have had prior anesthesia for orthopedic procedures prior to this surgery and may have been treated by the PI or Co-Investigators previously.

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.)
   N/A all subjects are within the study team's clinical practice.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   Subjects will be provided with a study brochure that will give a brief introduction about the study and its purpose. The brochure will contain the contact information for the study. This brochure may be given to the potential subject when they met with their surgeon and anesthesia provider, or it may be given to them at the PAT consultation that they have schedule to coincide with their date of surgery. A study team member will be available at the PAT appointment, or the potential subject may contact the study team directly through the contact information provided in the brochure. We will not cold call any patients who have not received a brochure. All subject will have ample time to review the consent form, whether they are signing it at the time of their PAT visit, or if they are signing it on the day of their signature. In either instance, the patient will have all their questions answered. Consents will be obtained in either a private exam room at PAT, or in a private pre-op exam room. Subjects will be provided a copy of the signed consent.

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.

   Subject will be required to demonstrate a clear understanding to the study team member consenting the subject by utilizing a "teach back" method. The study team member will assess their understanding by asking them to explain the study back to the study team member. Subjects must be able to demonstrate their understanding of the research study and be able to provide their own consent.

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.
   We will not enroll non-English speaking subjects.

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.) A waiver of signed consent is requested only for the purpose of reconsenting subjects with new procedure information. The waiver does not extend beyond this activity.

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 (activity) 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: We will obtain signed consent from all subjects who wish to participate.

☐ 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:

- What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Data to be collected from the medical record will include:
Age, gender, weight, height, BMI, ASA status, date of surgery, MRN, ethical background, laterality, preoperative medications, past medical history, surgical duration, daily opioid use, laboratory results (e.g. WBC, serum glucose), preoperative and postoperative daily minimum/maximum/average pain scores at rest and with activities, patient satisfaction of pain management and caregiver experience, any adverse events/complications, length of hospital stay, discharge disposition, hospitalization cost and length of rehabilitation stay if applicable. Additionally, we will be collecting the following patient self-reported outcomes from the medical record: Promis 10 score (all timepoints), Hoos Jr score (all timepoints), Koos Jr score (all timepoints), Baseline Employment Status, 6 Week Satisfaction, 12 Week Satisfaction, 12 Week Utilization, 12 Week Employment, Promis Pain Interference (all timepoints), Promis Physical Function (all timepoints).

Tools and Scales in functional status and surgical outcome include [1]. Boston mobility and daily activity scores (surrogate markers for functional status. Results of the above tools are in physical therapy, occupational therapy or orthopedic notes) [2]. patient-reported outcome measures (PROMs) [21,22] and assessment utilizing the Harris Hip Score (HHS) in surgeon's office at 6 weeks post op visit. Data will also be collected using the Brief Pain Inventory (Copyright 1991 Charles S. Cleeland, PhD, Pain Research Group). [23] The researchers will collect this data daily while the subjects are in the hospital.

In summary, data will be collected while patients are in the hospital, at 2 weeks via phone call and at 6 month chart review.

- How will the research data be collected, recorded and stored? Demographic data will be collected by the study research staff and recorded on paper (case report forms) as well as electronically. All information gathered for the research protocol will be archived in a secure, locked location. Only the PI and key study personnel with IRB and HIPPA training will have access to the information.

- How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server

- ☒Laptop Computer ☒Desktop Computer ☐Other

- 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 will be stored using codes that we assign. Data will be kept in password protected computers. Samples will be kept in locked storage. Only study investigators will have access to the data.

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

- 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 collected from this study will be secured and stored (with identifiers) for 5 years after the enrollment has been completed. After this period identifiers will be destroyed.

- 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.)

The findings from this study are unlikely to benefit the subjects participating in this study. The study findings will primarily benefit society, in which the knowledge gained from this comparison of analgesia for THA would potentially guide care to benefit others in the future.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   The alternative to participation is to not participate. Patients will still receive the standard of care analgesia which may be either of the two procedures being evaluated in the study.
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.

   Subjects will not receive any payment for study participation. All medications associated with this protocol are administered as standard of care for THA.

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.
   Research participation involves only assignment to one of the two standard of care analgesic options for THA, and data collection. Therefore, there is no additional cost associated with study participation beyond the standard of care expenses that the subject will incur as a result of their elective THA procedure.

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? Medical treatment will be available at YNHH/SRC while the subject is hospitalized for their standard of care surgery.
   b. Where and from whom may treatment be obtained? YNHH/SRC
   c. Are there any limits to the treatment being provided? No
   d. Who will pay for this treatment? The subject or his/her insurance carrier will be billed for the cost of treatment.

e. How will the medical treatment be accessed by subjects? Subject will be able to access care while inpatient during admission for surgery. Post discharge, the subjects will access care through the surgeon's office or emergency room if needed.

IMPORTANT REMINDERS

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

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

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

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

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

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

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

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

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

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

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

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