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NYU Langone Health

ADDUCTOR CANAL BLOCK PLUS IPACK BLOCK VS ISOLATED ADDUCTOR CANAL BLOCK FOR POSTOPERATIVE ANALGESIA IN ACLR WITH BONE PATELLAR TENDON BONE AUTOGRAFT

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NYULMC Study Number:	i22-00148
Study Product:	N/A

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

ACLR	Anterior Cruciate Ligament Reconstruction
BPTB	Bone Patellar Tendon Bone
IPACK	Interspace between the Popliteal Artery and Capsule of the Knee
ACB	Adductor Canal Block
ASA	American Society of Anesthesiologist Score
BMI	Body Mass Index
DOS	Day of surgery
VAS	Visual analog scale
AE	Adverse event
SAE	Serious adverse event
IV	Intravenous
ITT	Intention-to-treat
PACU	Post-Anesthesia Care Unit
PO	Taken orally
CI	Confidence interval
SD	Standard deviation; a parameter that characterizes a population distribution
SE	Standard error
ANOVA	Analysis of variance; a linear model
NSAID	Non-steroidal anti-inflammatory drug

Protocol Summary

Title	Adductor Canal Block and IPACK Block vs. Isolated Adductor Canal Block for Post-Operative Analgesia Following ACL Reconstruction with Bone Patellar Tendon Bone Autograft: A Single Center Randomized Placebo-Controlled Trial.
Brief Summary	A randomized, single-blind, single-center study measuring the effects of adductor canal block combined with IPACK infiltration compared to adductor canal block alone on post-operative pain and opioid consumption in patients undergoing ACL reconstruction with Bone Patellar Tendon Bone Autograft
Objectives	To determine if the addition of an IPACK block to the standard adductor canal block is superior to an isolated adductor canal block in controlling post-operative pain and decreasing postoperative opioid consumption in patients undergoing ACLR with Bone Patellar Tendon Bone Autograft
Methodology	Randomized, single-blind, single-center study
Endpoint	**Primary Endpoint:** Opioid utilization for the first 72 hours after surgery, including during surgery, calculated as morphine equivalent. **Secondary Endpoints:** Opioid consumption Post-operatively Patient reported VAS scores in PACU Length of stay in PACU Patient reported VAS scores on POD 1, POD 2, POD 3, POD 7 Reaction to IPACK block Incidence of postoperative complications
Study Duration	The study will continue until 50 subjects are enrolled per arm, to allow for potential dropout and increased power.
Participant Duration	Each participant will be enrolled on DOS and complete their final follow up on postoperative day seven.
Duration of IP administration	Once during surgery
Population	50 patients per study arm scheduled for ACLR with BPTB autograft
Study Sites	NYU Langone Orthopedic Hospital and NYU Ambulatory Surgery Center at 38th street
Number of participants	100
Description of Study Agent/Procedure	Patients in both the study and control group will receive the standard of care adductor canal block composed of 15 mL of Bupivacaine (0.25%). Patients in the study group will receive the additional IPACK block performed using 20 mL of Bupivacaine (0.25%) injected into the interspace between the popliteal artery and capsule of the knee. Patients will be blinded to their group allocation.
Reference Therapy	Reference is isolated adductor canal block
Key Procedures	Adductor canal block 15 mL 0.25% Bupivacaine, IPACK block with 20 mL 0.25% bupivacaine

Statistical Analysis	Continuous and categorical baseline characteristics will be compared using Hedges standardized difference. Normally distributed data will be compared using t tests while non-normally distributed continuous outcomes will be assessed using the Mann-Whitney U test.

1 Background and Specific Aims

Anterior cruciate ligament (ACL) reconstructions are among the most commonly performed outpatient orthopedic procedures, with approximately 400,000 ACLRs performed each year.[1] Outcomes following ACL reconstruction (ACLR) are excellent, with low rates of graft failure and high rates of return to pre-injury function.[2,3] Despite these positive outcomes, post-operative pain and discomfort is a commonly cited complaint following ACLR. Pain control following ACLR is multimodal, including peripheral nerve blocks intraarticular injections, oral, and IV medications.[4] However, given the rise in reported rates of addiction to opioids and high prescribing patterns among orthopedic surgeons, alternative pain control modalities must be explored.[4,5]

For arthroscopic ACLR with Bone Patellar Tendon Bone (BPTB) autograft, assuming there are no contra-indications, anesthesiologists at our institution perform a block of the saphenous nerve via the adductor canal, also known as adductor canal block (ACB). When compared to a femoral nerve block (FNB), the adductor canal block has been shown to have equivalent analgesia without the undesired quadriceps weakness associated with FNBs.[6-8] While these peripheral blocks have proven to be effective, they spare sensory function to the posterior knee compartment, leading to posterior knee pain postoperatively. This portion of the knee, innervated by the common peroneal nerve, obturator nerve, and tibial nerves, can be a source of pain for patients following knee surgery.[9] The IPACK block seeks to reduce pain in the posterior aspect of the knee, while sparing quadriceps strength. There have been several studies looking at the use of IPACK block in arthroplasty; these studies have found a short term improved analgesic effect of decreased pain scores while in the post anesthesia care unit (PACU), however they did not find significant differences in amount of narcotics used postoperativly.[6,9-11] In a study looking at ACLR with femoral block + IPACK and local infiltration anesthesia, patients who underwent IPACK and femoral block had lower postoperative IV morphine consumption within 24 hours of surgery.[12] To date, there have been no studies looking at analgesia using IPACK block combined with adductor canal block for patient undergoing ACLR in the ambulatory setting. With this blinded randomized control trial, we seek to elucidate the added benefit of an IPACK block and to determine if it leads to improved pain control and decreased opioid use following ACLR with BPTB autograft.

1.1 Specific Aims

This study will aim to compare ACB + IPACK block versus ACB only for posterior knee pain in patients undergoing ACLR with BPTB autograft.

AIM 1: To determine if the addition of IPACK block to the standard of care ACB is superior in terms of decreasing opioid consumption, decreasing pain, and increasing analgesia duration following anterior cruciate ligament reconstruction.

1.2 Statistical Hypothesis

We hypothesize that patients who receive an IPACK block plus an ACB will have lower postoperative opioid consumption over the first 24 hours (measured in morphine equivalents) compared to those who an isolated ACB following anterior cruciate ligament reconstruction. Furthermore, the study group will report lower postoperative pain scores on POD1 than the control group. Failing to reject the null would signify that the IPACK block has no clinically relevant difference on post-operative opioid consumption outcomes following ACLR with BPTB autograft.

1.3 Objectives and Purpose

The goal of this study is to determine if the addition of IPACK block to the standard of care adductor canal block is superior to an isolated adductor canal block in decreasing postoperative pain, decreasing opioid consumption, and leads to increased duration of analgesia in patients undergoing ACLR. The primary objective will be to compare opioid utilization between the two arms within the first 72 hours after surgery, including intraoperatively, as measured by morphine equivalents. Our secondary objectives are measuring patient reported pain scores in PACU at 24 hours, 48 hours, and 72 hours, and at the first postoperative visit (POD 7).

2 Study Design and Endpoints

Arm 1: Experimental	Arm 2: Control
Sample Size: 50	**Sample Size: 50**
Medication: 15 mL of 0.25% Bupivacaine block of the saphenous nerve injected under ultrasound guidance via adductor canal and IPACK block with 20 mL of 0.25% Bupivacaine injected into the Interspace between the Popliteal Artery and Capsule of the Knee	**Medication:** 15 mL of 0.25% Bupivacaine block of the saphenous nerve injected under ultrasound guidance via adductor canal

2.1 Description of Study Design

RECRUITMENT PHASE/CONSENTING PHASE:
Surgeons will identify eligible patients via Epic during their initial clinic visit and discuss the study. Surgeons will provide research coordinator with the name and medical record number of eligible patients. If the patient meets the inclusion criteria outlined below and is agreeable, subjects will be first introduced to the study during one of their presurgical clinic visits and then consented on the day of surgery by a member of the research team. Patients will be made acquainted with the study prior to surgery. On DOS when they arrive 1.5/2 hours before surgery, we (study team members) will consent them in a private room and provide ample time to discuss and review any questions or concerns they may have.

BASELINE ASSESSMENTS:
Subjects will complete a baseline VAS McGill Pain scale, Kujala, KOOS-PS and Tegner Activity Scale

RANDOMIZATION PHASE:
Subjects scheduled to undergo ACLR with BPTB autograft will be randomized to either ACB with IPACK block or to ACB only. A randomization scheme will be created prior to start of study enrollment using the randomizer.org website to generate the assignment. Block randomization is commonly used in clinical trial design to reduce bias and achieve balance in the allocation of participants to treatment arms throughout the course of the study. Randomized block design allows us to account for variables so that observed differences are largely due to true differences between treatments and not to the variable. We will create blocks of four patients and in each block, two patients will be assigned to the IPACK + ACB group, and two to the ACB only

group. Thus, patients in both groups with be evenly spread from the beginning to the end of the study.

A research coordinator will place the randomization results in sealed envelopes prior to recruitment. Each subject enrolled in the study will be assigned a number and the sealed envelope assigning the subject to the IPACK + ACB or ACB only will be opened on the day of surgery after the patient has signed consent agreeing to participate in the study.

Patients will be blinded to their group allocation. During peripheral block patients are sedated and postoperatively, the areas of infiltration will be covered by bandage.

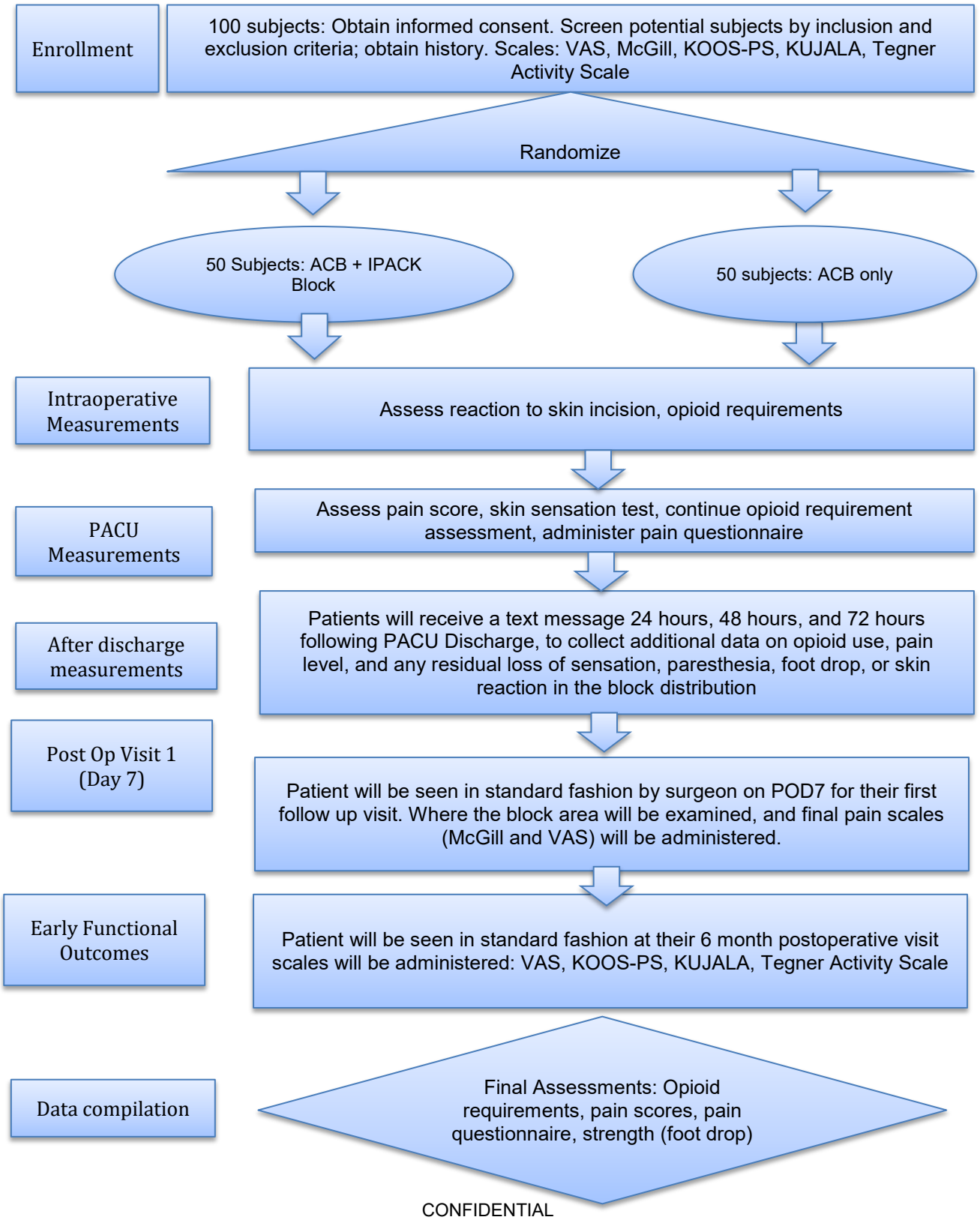
TREATMENT PHASE:

Patients in both the study and control group will receive the standard of care adductor canal block. This consists of 15mL of bupivacaine (0.25%) Injected under ultrasound guidance in the saphenous nerve via the adductor canal. Patients in the study group will receive the additional IPACK block performed using 20 mL of bupivacaine (0.25%) injected into the interspace between the popliteal artery and capsule of the knee.

POST-OPERATIVE PHASE:

After initial recruitment, subjects' pain will be assessed via visual analog scale (VAS) by nursing staff during the post-operative period as per standard of care in the post anesthesia care unit, and by the research staff prior to leaving the surgical center. The VAS pain scores are collected and documented in the patient's electronic medical record. Additionally, a standardized regimen of pain medication will be given to all subjects who are enrolled. The pain medications given to patients are standard of care medication 325-5 mg Percocet and vary based on pain level. This is determined by the clinical staff caring for each patient. While the patient is in the PACU prior to discharge, an authorized research member will visit the patient and obtain a pain score using the VAS and McGill Pain Scale. Data on PACU opioid use documented in the electronic medical record will be collected. On POD1, POD 2 and POD 3, a phone call or email survey will be sent to the patient to collect additional data on opioid use at home as well as a VAS score at 24, 48, and 72 hours after surgery.

2.2 Schematic of Study Design



3 Study Enrollment and Withdrawal

The researchers will approach patients scheduled for primary ACLR and are eligible for participation in the study. Anesthesiology/Sports Medicine attendings, fellows, residents, and authorized researchers will consent and enroll patients pre-operatively.

3.1 Inclusion Criteria

- Patients between 18 and 75 years of age
- Patients undergoing primary ACL reconstruction with BPTB Autograft
- ASA I or II

3.2 Exclusion Criteria

- Patients younger than 18 and older than 75.
- Patients with multi-ligament injury
- Patients undergoing concomitant cartilage procedure or osteotomy.
- Patients with a history of chronic pain that have used opioids for pain management for 3 months or longer.
- Patients who are allergic to oxycodone;
- Patients with diagnosed or self-reported cognitive dysfunction;
- Patients with a history of neurologic disorder that can interfere with pain sensation;
- Patients with a history of drug or recorded alcohol abuse;
- Patients who are unable to understand or follow instructions;
- Patients with severe liver disease, renal insufficiency, congestive heart failure, and/or significant heart disease;
- Patients with an allergy or contraindication to any of the medications used in the study, or patients with a contraindication to any study procedures;
- Patients with a BMI over 45;
- Any patient that the investigators feel cannot comply with all study related procedures;
- Any pregnant patient; assessed via urine pregnancy test in the preoperative area as part of standard preoperative surgical protocol;

3.3 Vulnerable Subjects

No vulnerable populations will be enrolled in this study.

3.4 Recruitment and Consent

Surgeon will identify potential subjects during their initial preoperative visit at which the surgeon will discuss the study with the patient. Should the potential subjects agree, the surgeon will provide the researcher with the name and medical record number of the patient. Researchers will receive the name and MRN of potential subjects identified by treating physician (study team members not volunteers) will utilize EPIC to extract patient demographic and surgical information to determine study eligibility. Once eligibility is confirmed, the treating physicians (TPs) will be notified via email, and they will discuss the study with the patient in the clinic at least 1 day prior to surgery to allow potential subjects to review and consider participation in the study.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact study coordinator or have subjects contact research-contact-optout@nyumc.org or 1-855-777-7858.

Written consent will then be obtained on the day of surgery in the preoperative holding area by an authorized research team member or the treating physician (surgeon or anesthesiologist). Once the patient is enrolled, they will be assigned a subject ID number and be randomized into a treatment group.

Once enrolled in the study, subject medical records will be accessed once more after surgery (for the second and final time) using subject MRNs by authorized study team members to collect demographic data including age, BMI, sex, smoking history, past surgical history, intraoperative findings, and opioid consumption (mgs) in the PACU. Once collected, deidentified data will be stored in the MCIT-managed HIPAA-compliant and encrypted version of Redcap in addition to the MCIT governed, firewall protected shared drive located on the NYU MCIT network.

Data linking protected health information to the deidentified patient record number will be kept in a local password-protected computer. Only the principal investigator will have access to the identified data.

Process of Consent
Written consent for participation will be obtained on day of surgery in pre-operative holding room by the Attending Physicians, or authorized researchers that are members of the study team. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and participants will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation suited to their comprehension of the purposes, procedures and potential risks as well as their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the key information form document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care will not be adversely affected if they decline to participate in this study. If possible, subjects will be given a copy of the informed consent form at their pre-surgical visit to allow them time to read through it, discuss with their relatives, and contact the study team with any questions prior to their surgery.

A copy of the signed informed consent document will be given to the patient, placed in the patient's electronic medical record and the original copy will be stored in the research regulatory binder. Any alteration to the standard consent process (e.g., use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Capacity will be assessed through the subject's ability to express understanding of the information being presented to them. The subject will be asked to state back the goals of the study and that they are willing to participate in their primary language.

3.5 Duration of Study Participation

The study will remain open until 50 patients are recruited for each intervention arm of the study. The actual subject participation length will be seven days.

3.6 Total Number of Participants and Sites

Recruitment will end when 100 participants have been enrolled. It is expected that there will be subjects enrolled who will be lost to follow up and be evaluated by intention-to-treat. The sites for enrollment will be the NYU Langone Orthopedic Hospital and NYU Ambulatory Surgery Center at 38th street.

3.7 Participant Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

3.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable; or
- Determination of futility

4 Study Procedures and Schedule

4.1 Study Procedures/Evaluations

4.1.1 Study Specific Procedures

Patients will be screened for eligibility by the surgical team during their pre-surgical office visit. Surgeons will explain the study to the eligible patient.

If patients are agreeable to participation, a research team member will provide further details and ask for participation on day of surgery. Informed consent will be obtained on day of surgery when the patient is in the pre-operative holding room by an authorized research member. Patient will complete a **baseline pain assessment as part of the research study.**

Patients in both the study and control group will receive the standard of care adductor canal block composed of 15 mL of bupivacaine (0.25%). Patients in the study group will receive the additional IPACK block performed using 20 mL of bupivacaine (0.25%) injected into the interspace between the popliteal artery and capsule of the knee. This use of bupivacaine (0.25%) in this dosage is consistent with its approved use for peripheral nerve blocks of the lower extremity, per the package insert.

Postoperatively, pain will be assessed via visual analog scale (VAS) by nursing staff during the post-operative period as per standard of care. The VAS pain scores are collected and documented in the patient's electronic medical record. Additionally, while the patient is in the PACU, an authorized research member will visit the patient and administer a pain questionnaire (VAS and McGill Pain scale). Data on PACU opioid use documented in EPIC will be collected.

4.1.2 Standard of Care Study Procedures

The subjects receiving standard of care procedures will undergo adductor canal block with 15 mL of 0.25% bupivacaine. Although not standard of care at this institution, the addition of IPACK block is widely accepted as a standard part of multimodal analgesia in ACLR.

4.2 Study Schedule

4.2.1 Screening

Screening Visit (Pre-surgical office visit -30 to -1 days)

- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Provide participants with further details regarding their participation on day of surgery and follow up.

4.2.2 Enrollment/Baseline

Enrollment/Day of surgery (Visit 1, Day 0)

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Complete baseline global health and pain assessment
- Randomize to ACB or ACB + IPACK group
- Perform surgery with analgesic intervention determined by randomization
- Record vital signs, opioid usage, results of examinations, other pain assessments.
- Continue observation in PACU preceding discharge, including administration of VAS scores, pain questionnaire, and opioid usage monitoring.

4.2.3 Follow-Up Phone call/message (POD 1, POD 2 and POD 3)

Phone call to patient to collect additional data on opioid use following discharge, on POD 1, POD 2 and 3 after surgery

4.2.4 Postoperative Visits

Patients will present to postoperative visit #1 of POD 7 per standard of care, at which point VAS pain, ROM, and strength will be assessed.

4.2.5 Withdrawal/Early Termination Visit

Subjects may discontinue their participation in the study at any time. As there is only a single intervention, and the safety of this is not in question, further follow up will not be required if a subject decides to terminate their participation in the study.

4.3 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

5 Risks and Benefits

5.1 Potential risks

Medication and Procedure

The potential risks associated with bupivacaine include neurologic and cardiac toxicity, if injected intravascularly. However, the risk is very low because a trained anesthesiologist using ultrasound guidance will perform both the IPACK block and ACB. US guidance allows the anesthesiologist to see and avoid blood vessels when administering the medication. Additionally, the syringe of the local anesthetic will be aspirated prior to injection by the anesthesiologist and surgeon to ensure that the block needle tip is not intravascular.

The risk of nerve injury or intravascular injection in the IPACK block is similar to the standard ACB arm of the study. Risk of infection at the injection site due to the expertise of the anesthesiologist performing the block under ultrasound guidance under sterile conditions to avoid infection risk. Allergic reactions to local anesthetic is possible however, any subjects with a history of allergies to local anesthetic will be excluded from the study.

At the time of the nerve block, the anesthesiologist who is providing the injection under ultrasound will monitor the subject's vitals, respiratory and cardiac status to assess for the aforementioned risk of neurologic or cardiac toxicity, as suggested in the Bupivacaine package insert Subsequently, patients will be monitored in the post anesthesia care unit per standard of care for any adverse effects of the nerve block including nausea, vomiting, blurred vision, and infection at the injection site. Both the ACB and ACB plus IPACK block are used as standard of care at this institution depending on treatment physician's preference.

5.2 Potential benefits

Study subjects may experience better pain control, improved satisfaction, decreased need for opioids and reduced incidence of side effects. If the study is not inconclusive, the study's results may benefit future patients by showcasing that addition of IPACK block improves pain control in the first 24 hours of an ACLR.

6 Statistical Analysis

6.1 General Approach

The primary analysis will follow the intention-to-treat (ITT) principle in order to evaluate the true outcome of the intervention as experienced by the patient who is blinded to the intervention.

Continuous and categorical baseline characteristics will be compared using Hedges standardized difference Normally distributed data will be compared using t tests while non-normally distributed continuous outcomes will be assessed using the Mann-Whitney U test.

It is anticipated that the data for some subjects will be incomplete for various reasons: missing diary entries, refusal to answer a question on the questionnaire, onset of illness, loss-to-follow-up, etc. All occurrences of incomplete data will be investigated to carefully document the reasons for the missing data. If the primary outcome (amount of opioid utilization for the first 24 hours after surgery) cannot be ascertained with a reasonable degree of certainty, the patient will be excluded from the study.

6.2 Analysis of Endpoints

Primary Endpoints:

1. Opioid utilization for the first 24 hours after surgery, including during surgery, calculated as oral morphine equivalent.

Secondary Endpoints:

1. Patient reported VAS scores in PACU
2. Length of stay in PACU
3. Patient reported VAS scores on POD 1, POD 2, POD 3, POD7
4. Reaction to IPACK block
5. Mid-term functional outcomes will be assessed at 6 months: VAS, KOOS-PS, KUJALA, Tegner Activity Scale, strength, ROM.

Normally distributed data such as the primary outcome variable will be compared using the two-sample t-test. In the case that the data are not normally distributed, the Wilcoxon rank-sum test will be used instead. Categorical variable will be compared using the Chi-Squares unless other tests such as the Fisher's exact test are more appropriate.

All endpoints will be evaluated as fits the data set with graphical figures such as scatter plots, box-and-whisker plots, and frequency histograms to visualize the distribution of these outcomes and their relationships to covariates and treatment assignment. When appropriate descriptive graphical and tabular methods will also be estimated and presented in a graphical figure.

6.2.1 Baseline Descriptive Statistics

The following patient data will be recorded: age, gender, height, weight, MRI diagnosis date of admission, date of discharge, laterality, surgical approach, implants used, duration of surgery, concomitant procedure, contamination, ASA, comorbidities (smoking, cardiac history, diabetes etc.), and medications. This information will be accessible in the patient's medical record.

6.3 Sample Size

Using a 2-sided, 2-sample t test, an α value of 0.05, a power analysis revealed that 42 subjects were needed per group to detect a moderate effect size with a power of 0.80. We chose to enroll 50 subjects per arm to allow for potential dropout and an increased power.

6.4 Enrollment/Randomization/Masking Procedures

We will utilize randomization.com to generate a block randomization assignments for all 100 participants. Someone that is not a stakeholder in the study will make randomization envelopes, which include the study ID number, the treatment assignment, and dosage specifics. These randomization envelopes will then be distributed to the anesthesiologist pre-operatively by the authorized researcher after informed consent is obtained.

6.5 Breaking the Study Blind/Participant Code

If there is any adverse event related to the drug, we will break the blind for the subject and randomization will be disclosed to the patient.

7 Assessment of Safety

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1 Definition of Adverse Events (AE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.2 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e., 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

7.3 Classification of an Adverse Event

7.3.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.3.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

1. ***Related*** *– The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.*
2. ***Not Related*** *– There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.*

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

1. ***Definitely Related*** *– There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.*
2. ***Probably Related*** *– There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.*
3. ***Possibly Related*** *– There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.*
4. ***Unlikely to be related*** *– A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).*
5. ***Not Related*** *– The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.*

7.3.3 Expectedness

The PI, Dr. Strauss, will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

7.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

7.5 Reporting Procedures – Notifying the IRB

7.5.1 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

1. Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
2. A detailed description of the event, incident, experience, or outcome;

3. An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
4. A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 7 days of the IR's receipt of the report of the problem from the investigator.

7.6 Safety Oversight

It is the responsibility of the Principal Investigator Eric J Strauss, and co-investigators David Furgiuele MD and Jovan Popovic MD to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Adverse Events such as development of an allergy to local anesthetic, inadvertent intravascular injection of local anesthetic and infection at site of injection will be reviewed every three months. Serious adverse events are rare and are unlikely to occur but if a serious adverse event occurs, steps will be taken to address it. Study recruitment will cease temporarily while a data safety monitoring team convenes to review the event. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Data Safety Monitoring Plan

The principal investigator Eric J Strauss, and co-investigators David Furgiuele MD and Jovan Popovic MD are responsible for data safety and monitoring of the overall study.

The following data points and outcomes will be reviewed during data safety monitoring reviews: number of patients enrolled, pain scores of patients, AEs and SAEs such as neuro and cardiotoxicity. Data will be monitored quarterly and will be reported at the time of continuing review.

The stopping rules for the study are adverse harm to patients, as measured by the serious adverse events, specifically neurotoxicity, cardiotoxicity, or allergic reaction to bupivacaine. A chi-square test will be used to determine if there is a statistically significant difference ($p<0.01$) in the rate of SAEs between treatment arms. If there is a statistically significant difference in the rates of SAEs between arms, accrual to the trail will be suspended while the study team and data safety monitoring team conduct an evaluation of the events.

The PI will oversee all study activities including data collection and management and will ensure study personnel conduct this study based on the approved protocol.

8 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and

office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records and patient contact will be limited to IRB-approved study team members, not volunteers. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

9 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

10 Ethics/Protection of Human Subjects

10.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

10.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

10.3 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

11 Data Handling and Record Keeping

11.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source

documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Redcap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

11.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication.

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

11.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to

register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

12 Study Finances

12.1 Funding Source

There is no funding source available.

12.2 Costs to the Participant

There are no expected costs to the subjects.

12.3 Participant Reimbursements or Payments

Participants will not receive any financial compensation for participation in this study.

13 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

14 References

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15 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

15.1 MORPHINE EQUIVALENTS

Analgesic	Path	Oral dose (mg)	OME (mg)	Conversion factor
Morphine	Oral	15	15	1
	Parenteral	5	15	3
Codeine	Oral	100	15	0.15
	Parenteral	60	15	0.25
Dihydrocodeine	Oral	100	15	0.15
	Parenteral	60	15	0.25
Hydrocodone	Oral	10	15	1.5
Hydromorphone	Oral	4	15	3.75
	Parenteral	1.5	15	10
Methadone	Oral	5	15	3
	Parenteral	5	15	3
Oxycodone	Oral	10	15	1.5
Propoxyphene	Oral	100	15	0.15
Tapentadol	Oral	60	15	0.25
Tramadol	Oral	67.5	15	0.222222
Fentanyl	Intravenous	0.1	15	150
	Transdermal	0.6	90	25
Pethidine	Oral	150	15	0.1
	Parenteral	50	15	0.3
Dextropropoxyphene	Oral	100	15	0.15

OME: Oral morphine equivalent.