Protocol Title: 4-drug Nerve Block versus Plain Local Anesthetic for Knee and Hip Arthroplasty Analgesia in Veterans

Protocol Version 10.0

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1.0 Specific Aims

Specific Aim

To compare the pain relief effects of plain bupivacaine nerve blocks against the effects of a 4-drug nerve block (bupivacaine-clonidine-buprenorphine-dexamethasone) for total knee or hip arthroplasty (TKA/THA). The survey instrument for the specific aim of the research (Short-Form McGill Pain Questionnaire, version 2, at 24 hr after surgery), is robust, valid, and reliable for evaluation of this important patient-centered quality-of-care parameter.

Exploratory Aims:

The secondary aims of short- and long-term physical therapy and rehabilitation-related benefits will also be examined for effects of nerve block drug treatment (plain bupivacaine versus 4-drug blocks) and surgical site (TKA/THA). The tertiary aim is to determine differences in opioid-related side effects based on nerve block treatment. Optimizing the described aims (ensuring that sufficient nerve block pain management duration does not compromise short- and long-term physical therapy efforts) is what we forecast that this comparative study will provide for future hypothesis generation, including the possibility that the 4-drug nerve block concept is adopted into general clinical practice.

2.0 Background and Significance

2.1 Background

The surgical invasiveness of elective total knee/hip arthroplasty (TKA/THA) in veterans provides a logical model under controlled conditions for evaluating physical therapy / occupational therapy (PT/OT) effectiveness after major lower extremity polytrauma sustained in the battlefield. The central idea of this protocol (in the grant application submitted to the Department of Defense) is to measure pain (primary) and rehabilitation (exploratory) outcomes after TKA/THA as influenced by factors under the direction of the anesthesiologist physician, specifically nerve block drug selection (plain bupivacaine versus the described 4-drug mixture as single-injection nerve blocks).

For these TKA/THA cases, our standard of care regional anesthesia (RegA) technique entails spinal anesthesia to ensure adequate anesthesia and excellent surgical conditions during surgery. Spinal anesthesia alone does not provide any sustained pain relief after surgery. As a result, our institutional standard of care for TKA/THA also entails single-injection nerve blocks (with the described 4-drug combination) of both L2-L4 and L4-S3 nerves/plexi, placed before surgery. Applying these nerve blocks before surgery ensures that our patients do not have significant pain after the spinal anesthetic "wears off" later in the day after surgery.

Nerve blocks can be administered as single-injections or via percutaneous indwelling catheters, the latter of which being far more labor-intensive and expensive.(1) We do not use indwelling perineural catheters at our institution. In the absence of the described 4-drug **M**ulti**M**odal **P**eri**N**eural **A**nalgesia (MMPNA), the plain bupivacaine single-injection (0.1% - 0.25%) nerve block is typically reported as having 8-16 hr analgesic duration. In our institutional standard of care experience, the addition of clonidine-buprenorphine-dexamethasone (CBD) to bupivacaine 0.1% – 0.25% yields an average duration of analgesia of approximately 36 hr. We are unable to determine if this additional analgesic duration inhibits physical therapy after surgery (one of our exploratory aims for this specific study).

"Nerve block analgesia" is not necessarily synonymous with "nerve block numbness." Analgesia is "pain relief," and pain relief without numbness is thought to promote early physical therapy. Nerve block numbness (even though the numbness is indeed providing pain relief) is expected to delay physical therapy due to lack of muscle strength during numbness. One of the goals of the study's exploratory aims is to determine if the MMPNA 4-drug combination provides both improved pain relief and improved physical therapy in the days after surgery (when compared with plain bupivacaine).

Anesthesia planning for invasive orthopedic surgery after battlefield-sustained polytrauma above and below the abdomen typically requires general endotracheal anesthesia (GETA) for surgical stabilization of all traumatic injuries. However, based on recent anesthetic innovations, GETA is no longer required for elective TKA/THA, and therefore GETA is not specifically required for one-sided lower-extremity polytrauma. For TKA/THA, the exclusive use of RegA (without GETA) is not only feasible and sufficient, but also comparatively effective via reductions in morbidity and mortality (based on population data).(2) GETA has temporary adverse effects on immediate postoperative cognitive function after surgery, and the cognitive risks after multiple episodes of GETA is unknown but is unlikely to be beneficial long term. Eliminating GETA as a confounder of immediate physical therapy / occupational therapy (PT/OT) outcome evaluation now allows for proper evaluation of anesthesiologist physician-directed pain relief, and this study of veteran-specific care has the potential to immediately translate to the care of injured military personnel.

This is a prospective randomized clinical trial comparing the two nerve block treatments described above. MMPNA (used in the 4-drug treatment which is our current institutional standard of care) entails nerve block drug combinations using all preservative free and commercially-available injectable drugs. Clonidine-buprenorphine-dexamethasone (CBD) are off-label; each individual drug has achieved textbook status (3-5) for routine clinical use in nerve blocks after appropriate clinical efficacy being demonstrated in clinical trials during the past 15-20 years. The PI's research team has demonstrated *in vitro*(6) and *in vivo*(7) safety of *combined* CBD with local anesthetics. FDA approved local anesthetics (e.g., bupivacaine) are among the "gold standard" drugs used for peripheral nerve blocks. To date, there have been no "head-to-head" publications comparing MMPNA (4-drug block) versus plain local anesthetic.

2.2 Preliminary Studies

Since July 2011, our center (VA Pittsburgh Healthcare System) has routinely used MMPNA with CBD (with bupivacaine) for its peripheral nerve blocks postoperative analgesia (in addition to the intraoperative spinal anesthetic for reliable surgical anesthesia). We have since published our observed outcomes for these patients (*Pain Medicine* 2015, ref.9), which was a median analgesic duration of 37 hr (95% confidence interval of the mean being 30-49 hr).

The duration of nerve block analgesia (as opposed to "numbness" or motor block) is important since longer duration appears to attenuate patient's "rebound pain"(11). Since CBD are "motor sparing" analgesic adjuvants to local anesthetics used in nerve blocks, CBD added to bupivacaine will help extend the duration of analgesia, but would not necessarily prolong motor block. We anticipate that higher rebound pain scores will inhibit the achievement of postoperative PT/OT objectives.

2.3 Significance

In our attempt to eliminate the effects of traditional GETA confounding the progress of PT/OT after TKA/THA, we aim to demonstrate that the "4-drug blocks" have significant clinical benefit over blocks with plain bupivacaine. These benefits should be immediately transferable to active military personnel injured in battle and presenting to the operating theater for surgery on the traumatized lower extremity, in efforts to minimize immediate pain along with the risks of joint contracture and stiffness during long-term PT/OT efforts after surgery. This paradigm shift in RegA (specifically, the described 4-drug MMPNA combination) is innovative, inexpensive, and provides the potential for distinct advantages over complex and labor intensive nerve block catheter techniques.

3.0 Drug Information

3.1 Bupivacaine combined with CBD:

This protocol's study treatment will use bupivacaine-based MMPNA in which CBD is added to bupivacaine. Plain bupivacaine will be used as the active control (there will be no placebo group). Bupivacaine is FDA-approved for use as a local anesthetic. MMPNA entails nerve block drug combinations using all preservative free and commercially-available injectable drugs. The individual drugs comprising CBD are off-label; each has achieved textbook status (3-5) for routine clinical use in nerve blocks after appropriate clinical efficacy being demonstrated in clinical trials during the past 15-20 years.

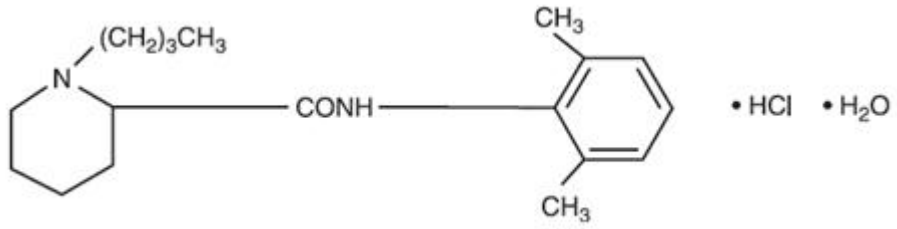
3.2 Bupivacaine (12)

Clinical Uses

Bupivacaine hydrochloride injection, USP is indicated for the production of local or regional anesthesia or analgesia for surgery, oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures.

Chemistry and Metabolism

Bupivacaine hydrochloride USP is 2-Piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white, odorless, crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Bupivacaine hydrochloride injection, USP is available in sterile isotonic solution for injection via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Solution of Bupivacaine hydrochloride injection, USP may be autoclaved. Solution is clear and colorless.

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain

an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

Bupivacaine hydrochloride injection, USP — Sterile isotonic solution containing sodium chloride. The pH of the solution is adjusted to between 4 and 6.5 with sodium hydroxide or hydrochloric acid.

Pharmacokinetics

The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of Bupivacaine, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with Bupivacaine is rapid, and anesthesia is long lasting. The duration of anesthesia is significantly longer with Bupivacaine than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.

Although not applicable to this study, local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. Bupivacaine with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, non-ionized drugs readily enter the fetal blood from the maternal circulation.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profile of Bupivacaine after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of Bupivacaine hydrochloride for caudal, epidural, or peripheral nerve block in man, peak levels of Bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant

levels during the next three to six hours. For this study, peripheral nerve block (not caudal or epidural) is the basis of the specific aim.

Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of bupivacaine in adults is 2.7 hours (and in neonates 8.1 hours).

In clinical studies, elderly patients reached the maximal spread of analgesia and maximal motor blockade more rapidly than younger patients. Elderly patients also exhibited higher peak plasma concentrations following administration of this product. The total plasma clearance was decreased in these patients.

Amide-type local anesthetics such as Bupivacaine are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of Bupivacaine.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of Bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, Bupivacaine hydrochloride does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

3.3 Clonidine

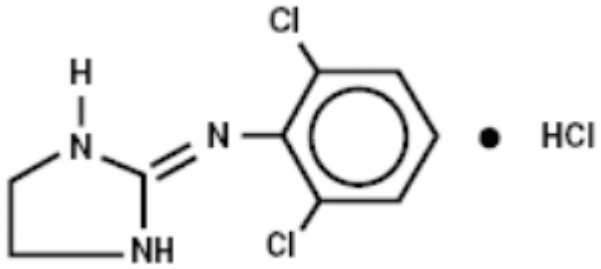
Clinical Uses

Clonidine is a drug that is commonly used for its analgesic effects on the central nervous system, providing dose-dependent analgesia. Clonidine is most often used in epidural / intrathecal catheters for continuous infusion; however, in the field of anesthesiology (in the operating room). it is commonly used in perineural injection as a peripheral (not central) adjuvant to local anesthetics. (13) The spinal cord and epidural space (the use of clonidine for which it is FDA-approved) is generally accepted to be at much higher risk of local drug toxicity than in the peripheral nerve. In other words, the spinal cord / epidural space is much more “fragile” or “delicate” than is the peripheral nerve, with clonidine use in the spinal column being FDA-approved. The chemical names of clonidine are Benzenamine, 2,6-dichloro-N-2-imidazolidinylidene monohydrochloride and 2-[(2,6-dichlorophenyl) imino]-imidazolidine monohydrochloride, and its structural formula is shown below.

Clonidine has been used as an additive to various local anesthetics in peripheral nerve blocks as a means of prolonging the duration of analgesia after surgery. (14, 15) Clonidine added to local anesthetics is thought to provide an additional 100 minutes of analgesia.(14) It has also been reported that clonidine and buprenorphine have been used *in the absence of local anesthetics* in order to provide perineural analgesia. (16) The mechanism of action of clonidine appears to be partially related to the I_h hyperpolarization current (17), with an apparent additional analgesic action related to C-fiber compound action potential attenuation. (18)

Chemistry and Metabolism

Clonidine that is supplied for injection is a clear, colorless, preservative-free, aqueous sterile solution. Clonidine metabolism follows minor pathways with the metabolite, p-hydroxy-clonidine, and is less than 10% of the concentration of the drug in urine. (13)



Pharmacokinetics

A clinical examination of the clearance rate of clonidine with 5 male subjects who received a 10-minute intravenous infusion of 300 mcg of clonidine shows that clonidine two distinct phases: one in which clonidine rapidly distributes, and a second slower phase in which the clonidine is eliminated from the body. The clearance rate of intravenous clonidine in this clinical study was 219 ± 92 mL / min. (13) The total perineural clonidine dose to be used in this study is 50 mcg (25 mcg in each of 2 peripheral nerve-plexus blocks).

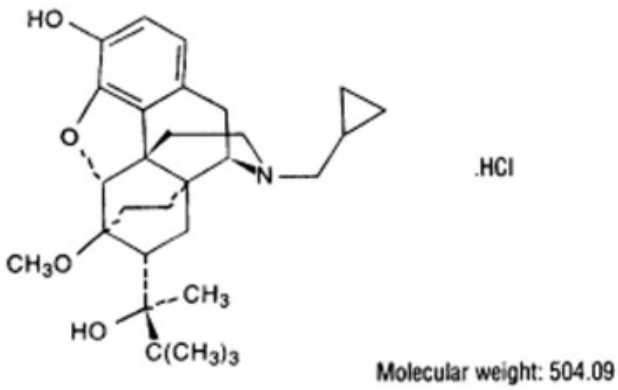
3.4 Buprenorphine

Clinical Uses

Buprenorphine is an opioid which is used for its analgesic properties and is intended for intravenous or intramuscular administration. The chemical name of buprenorphine is 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4, 5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5α, 7α(S)] ,and its structural formula is shown below. (12) The mechanism of buprenorphine perineural analgesia is likely related to peripheral nerve opioid receptors. (13) Studies by Candido et al. (16, 17) show that the addition of buprenorphine to local anesthetics such as mepivacaine and tetracaine (along with epinephrine) prolongs the analgesic effects of the local anesthetics.

Chemistry and Metabolism

Buprenorphine hydrochloride is a white powder, weakly acidic and is slightly soluble in water, while the marketed form Buprenex (and since-available generic products) is a clear injectable liquid. (14)



Molecular weight: 504.09

Pharmacokinetics

Buprenorphine is metabolized by the liver, and its clearance is due to hepatic blood flow. The onset of analgesia from buprenorphine can take as little as 15 minutes.(14) As mentioned above, perineural injections of buprenorphine added to clonidine in the absence of local anesthetics have anecdotally provided 6-8 hrs of motor sparing analgesic, with a moderately fast onset of analgesic activity.

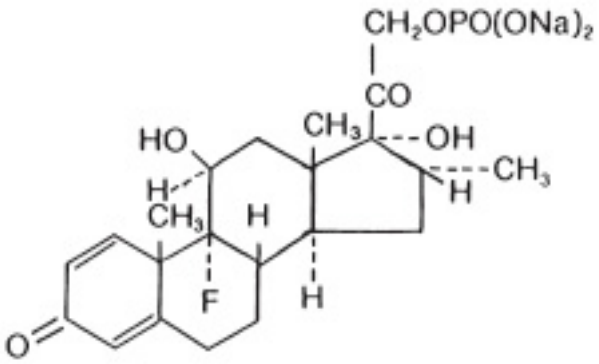
3.5 Dexamethasone (Dexamethasone sodium phosphate)

Clinical Uses

Dexamethasone is an adrenocortical steroid anti-inflammatory drug that is used for injection: intravenous, intramuscular, intra-articular, soft-tissue, and intralesional. The chemical name of dexamethasone is 9-Fluoro-11ß,17,21-trihydroxy-16α-methylpregna-1, 4-diene-3,20-dione 21-(dihydrogen phosphate) disodium salt, and its structural formula is shown below. (19) The mechanism of action is unclear however, it has been suggested that there is C-fiber attenuation with corticosteroids. (20)

Chemistry and Metabolism

Dexamethasone sodium phosphate is derived from dexamethasone of which it is an ester. The physical characteristics of dexamethasone are such that it occurs as a yellow crystalline powder that is soluble in water. (19)



$C_{22}H_{28}FNa_2O_8P$ M.W. 516.41

Pharmacokinetics

Once injected the onset of analgesia of dexamethasone is quite rapid, however the duration of analgesia of dexamethasone alone is relatively short. (19)

3.6 Drug Doses and Preparation

- **For diabetics** (known in advance): one 20 mL syringe **for the L2-L4 block**
    - If randomized to receive bupivacaine only:
        - Bupivacaine 0.5% 8mL
        - 0.9% sodium chloride 12mL
        - Resulting in a total volume of 20mL
        - The resulting net bupivacaine concentration is 0.2%
    - If randomized to receive bupivacaine plus clonidine-buprenorphine-dexamethasone:
        - Bupivacaine 0.5% - 8mL
        - Dexamethasone 10mg/1mL– 0.1mL
        - Buprenorphine 300mcg/1mL- 1mL
        - Clonidine 25mcg/0.25mL-0.25mL
        - 0.9% sodium chloride-10.65mL
        - Resulting in a total volume of 20mL and net bupivacaine concentration of 0.2%

- **For non-diabetics** (known in advance): one 20 mL syringe **for the L2-L4 block**
    - If randomized to receive bupivacaine only:
        - Bupivacaine 0.5%-10mL
        - 0.9% sodium chloride-10mL
        - Resulting in a total volume of 20mL and net bupivacaine concentration of 0.25%
    - If randomized to receive bupivacaine plus clonidine-buprenorphine-dexamethasone:
        - Bupivacaine 0.5%- 10mL
        - Dexamethasone 10mg/1mL– 0.1mL
        - Buprenorphine 300mcg/1mL- 1mL
        - Clonidine 25mcg/0.25mL-0.25mL
        - 0.9% sodium chloride- 8.65mL
        - Resulting in a total volume of 20mL and net bupivacaine concentration of 0.25%

- **For all L4-S3 blocks (irrespective of diabetes)**
    - If randomized to bupivacaine only:
        - Bupivacaine 0.5%- 4mL
        - 0.9% sodium chloride – 16mL
        - Resulting in a total volume of 20mL and a net bupivacaine concentration of 0.1%
    - If randomized to receive bupivacaine plus clonidine-buprenorphine-dexamethasone:
        - Bupivacaine 0.5%- 4mL
        - Dexamethasone 10mg/1mL– 0.1mL
        - Buprenorphine 300mcg/1mL- 1mL

- Clonidine 25mcg/0.25mL-0.25mL
- 0.9% sodium chloride- 14.65mL
- Resulting in a total volume of 20mL and a net bupivacaine concentration of 0.1%

3.7 Preparation of clonidine, buprenorphine and dexamethasone for administration

Preparation of clonidine-bupivacaine-dexamethasone-buprenorphine combination syringe:
Within 1 hour of (prior to) nerve block administration, the required quantities of injectable preservative free bupivacaine, buprenorphine, and dexamethasone will be withdrawn from single use containers and injected into an empty syringe. A single dose syringe of injectable clonidine will be added to this syringe along with a sufficient quantity of preservative free 0.9% sodium chloride to provide a total volume of 20mL.

Preparation of bupivacaine-only syringe:
Within 1 hour of (prior to) nerve block administration the required quantity of injectable preservative free bupivacaine will be withdrawn from a single use container and injected into an empty syringe. A sufficient quantity of preservative free 0.9% sodium chloride will be added to the syringe to provide a total volume of 20mL.

All drugs will be prepared on our nerve block cart, using our institutional standard of care process that entails hat and mask for the preparer, hand antisepsis with an isopropyl alcohol based skin cleanser, and cart-surface antisepsis with hospital approved antiseptic wipes. The preparer of the syringes (an experienced and trained member of the anesthesia care team with respect to preparation of such syringes) will otherwise be uninvolved with the study or with the involved patient.

4.0 Research Design and Methods

4.1 Type of Study

This is a single-site study that will take place at VA Pittsburgh Healthcare System, Pittsburgh, PA. It is a prospective randomized clinical trial evaluating the two different nerve block injection drugs for TKA and THA, introduced above and described further below. All described RegA techniques strategically avoid GETA and high-dose opioids, and the immediate postoperative complications (from GETA and high-dose opioids) that inhibit full-capacity cognitive function needed to accomplish PT/OT goals during the first 2 days after TKA/THA. Two hundred (200) total patients will be recruited and evaluated for study outcomes pre-TKA/THA (100 for TKA, 100 for THA). Following pre-surgical evaluation, patients will be block-randomized (stratified by [a] TKA vs. THA surgical procedure, [b] age, and [c] presence of diabetes). After surgery, all patients will undergo the same standardized PT/OT best-evidence care plans consistent with current clinical care at our institution. Evaluation of study outcomes will take place during the first two days after surgery, throughout the remainder of the hospital stay (which typically ranges from 2 to 5 days, including discharge day), and during the first two orthopedic post-op follow-up evaluations. The primary outcome is pain at 24 hr after surgery, and exploratory outcomes include physical therapy progress and anesthesia-related symptoms. We will also assess additional metrics of anesthesia and physical therapy success such as range of motion, physical function and performance testing, length of hospital stay, discharge placement, readmission, falls, and other adverse events.

Study Treatment Groups:

Institutional Standard of Care (ISOC)

All patients will receive a standardized bupivacaine spinal anesthetic, consistent with current institutional practice. All patients will receive pre-medications for the prevention of pain, nausea, vomiting, and gastroesophageal reflux, consistent with current institutional practice. All patients will receive intravenous hydration, intravenous antiemetics, and intravenous blood pressure support (e.g., intravenous phenylephrine bolus/infusion) consistent with our current institutional practice. The need for intraoperative blood transfusion will occur based on current institutional practice and collaborative decision-making between the surgical and anesthesia teams, consistent with current institutional practice.

ISOC MMPNA Block Group (n=80 TKA and 80 THA patients) will receive the ISOC 4-drug MMPNA nerve blocks at the L2-L4 and L4-S3 nerves/plexi. These blocks will be placed before the administration of spinal anesthesia, per our ISOC.

Active Control Block Group (n=20 TKA and 20 THA patients) will receive "active control" nerve blocks comprised of plain bupivacaine. As with the ISOC MMPNA Block Group, these blocks will be placed before the administration of spinal anesthesia, per our ISOC. Again, these blocks will involve the same L2-L4 and L4-S3 nerves/plexi as those for the ISOC MMPNA Block Group.

All study team members will be blinded to the nerve block treatment group/drug the patient receives/received for the described blocks. The only unblinded person regarding the study treatment will be the anesthesia team member who prepares the nerve block injection syringes, based on the randomization envelope assignment. This person who prepares the drug syringes will be otherwise uninvolved with the care of the study patient.

Table 1. Anatomic location of the analgesic nerve blocks used based on TKA versus THA

Basic description of regional anesthesia and analgesia care plan	TKA block details	THA details
Spinal anesthesia, L2-L4 and L4-S3 perineural/plexus single-injection nerve blocks	L2-L4 nerve block entails the femoral nerve in the groin. The L4-S3 nerve block entails the sciatic nerve as it emerges from the sciatic notch deep to the gluteal musculature.	L2-L4 plexus block entails the lumbar plexus within the psoas compartment, 2-3 inches lateral to the lumbar spine midline. The L4-S3 plexus block entails the lumbosacral trunk and parasacral plexus, which lies lateral to the lateral margin of the proximal sacrum. The plexus lies deep to the sacroiliac ligament.

4.2 Randomization and Blinding

A total of 44 randomized blocks are needed for the study. For random assignment and sequencing purposes, each randomized block consists of five integers that correspond to the four treatment and one control group assignment. The VA Pittsburgh Investigational Drug Service (IDS) Pharmacist will randomly determine which integer corresponds to the control group and the integers corresponding to the

four treatment groups; this random assignment will only be done once, and the same integers will correspond to the assigned groups across all blocks. The Investigational Drug Service Pharmacist will use a randomizer function available on www.random.org. In order to maintain the blind, the control and treatment group assignments will not be divulged to any study staff other than the anesthesia care team member who prepares the nerve block injections. The sequence of treatment/control assignments within each of the randomized blocks will be determined by the VA Pittsburgh StatCore using the sequence generator at website random.org. Each block will have a separate sequence generated for it.

The randomization scheme will be prepared before the start of the trial. Sequentially numbered and sealed envelopes containing the randomized control or treatment group assignment will be provided by the Investigational Drug Service (IDS) Pharmacist. The IDS Pharmacist will retain the sealed envelopes and will be responsible for providing them to the PI or designee as requested prior to the scheduled procedure. The PI or designee will then provide the sealed envelope to the nerve block drug mixer. The IDS Pharmacist will coordinate the provision of the nerve block drugs. The drugs will be stored in an automated dispensing cabinet and accessible only to the designated nerve block mixers.

After a subject has been enrolled, the study coordinator will submit a Treatment Allocation Request form to the IDS Pharmacist.

1) The Treatment Allocation Form will indicate the subject's criteria:
   a) Age: ≤69 or >69 years
   b) Type of procedure: total knee replacement or total hip replacement
   c) Diabetes status: present or absent
2) Based on the criteria noted on the Treatment Allocation Request form, the IDS Pharmacist will provide the next available treatment assignment envelope.
3) The IDS Pharmacist will also provide the mixer with a form to document the details of the nerve block drugs mixed, e.g., date and time of preparation, preparer's name, and drugs utilized.

Prior to the procedure, the mixer will open the sealed envelope to determine the treatment assignment. The mixer will prepare the assigned nerve block as per the established preparation guidelines and complete the accompanying documentation form. The re-sealed treatment assignment envelope and documentation form will ultimately be returned to the IDS Pharmacist, to prevent any inadvertent un-blinding of the treatment assignment.

4.3 Study Visits & Procedures

Study Visits:

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 1 and described in the text that follows. Additional information is provided in the manual of operating procedures.

The study team will attempt to coordinate all of the research questionnaires and physical therapy sessions with the patient's other inpatient and outpatient appointments at VAPHS. However, if this is not possible, the patient will be required to come in for additional visits to complete the research surveys and physical tests at the described study time-points. The total additional time required for the subject participating in this research study is approximately 4-5 hours (not including transportation to and from VAPHS). Patients participation in this study will be approximately 3-4 months and will consist of 1-2

visits prior to surgery, the day of surgery visits (pre- and post- surgery), their in-hospital post-surgery visits and two follow-up visits, scheduled in conjunction with their standard of care ortho scheduled post-surgery visits.

After surgery, all patients will undergo the same standardized PT/OT best-evidence care plans (knee-specific, and hip-specific, respectively) consistent with current clinical care at VA Pittsburgh Healthcare System.

Throughout the study and after the patient signs consent, if the patient is signed up to use the VA MyHealth*e*Vet online tool, communication between the patient and study team can occur using the secure messaging tool offered through MyHealth*e*Vet.

Screening/Baseline Visits

The screening and baseline visit can be completed on the same day, if feasible. No research screening or baseline procedures can be conducted until informed consent is complete.

Baseline assessments will include demographics (including age and weight), smoking status, diabetes status, comorbidity (CIRS: cumulative illness rating scale), completion of research questionnaires, and completion of physical therapy procedures.

If a patient has a significant health status change after the baseline visit, but before the scheduled surgery, the study team will evaluate the patient's current medical status and determine if the health status change will affect the baseline data. In the rare occasion that the study team determines the patient's baseline data will be affected, the patient will be asked to come back to the clinic for a second baseline visit. The patient will be compensated for this visit and all baseline procedures will be repeated. As this repeated baseline visit is for data integrity only, and not for safety purposes, if the patient refuses to come back in for the repeat baseline visit, they will not be removed from the study. The study team will document this as a minor protocol deviation and the patient will continue on the study as previously planned. .

Prior to the day of surgery, the patient will complete a standard of care IMPACT visit. (IMPACT: VAPHS preoperative clinic – Interdisciplinary Medical Perioperative Assessment Consultation and Treatment).

Day of Surgery

On the day of surgery, the patient will receive anesthesia/study drug. Research questionnaires will be completed pre- and post-surgical procedure. Please refer to Appendix 1 for additional details.

In-Hospital Post-op Days (1-5)

Post-op in hospital visits will occur while the patient is in the hospital.

Follow-up visits 1 and 2

These two visits will be done in conjunction with the patient's standard of care orthopedic post-op visits.

Study Procedures:

Study Questionnaires:

Short-Form McGill Pain Questionnaire (SF-MPQ) – version 2 (Specific Aim)

The SF-MPQ questionnaire will be used to measure the subject's knee or hip pain. The questionnaire consists of 15 different qualities of pain and related symptoms, in which the subject is asked to rate the intensity of each symptom on a scale (none, mild, moderate, or severe). The questionnaire also includes two additional items relating to the patient's current pain. This questionnaire takes 5-10 minutes to complete.

SF-8 Survey

The SF-8 Health Survey is a short 8-question survey designed to measure the patient's overall health at 24-hour intervals. It takes less than 3 minutes to complete (21).

Short-Form 36 Health Survey (SF-36)

The Short Form (SF) 36 Health Survey is a 36-item, patient-reported survey of patient health at one-month intervals. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. The questionnaire takes approximately 5-10 minutes to complete.

QoR-15 Questionnaire:

The QoR-15 form is a 15 question survey that evaluates the quality of recovery (QoR) after anesthesia. The QoR-15 short-form questionnaire was created using extensive clinical and research experience with the 40-item QoR-40 questionnaire (with which the PI has prior research experience), and taking the strongest psychometrically-performing items from each of the five dimensions of the QoR-40 to create a short-form version (22). The QoR-15 was evaluated in 127 adult patients after general anesthesia and surgery (22). It performs well in all dimensions, and takes about 2.5 minutes to complete (22).

Opioid-Related Symptom Distress Scale (ORSDS)

The Opioid-Related Symptom Distress Scale (ORSDS) is a 4-point scale that evaluates 3 symptom distress dimensions (frequency, severity, bothersomeness) for 12 symptoms (23). The symptom-specific ORSDS is the average of the 3 symptom distress dimensions (23). The composite ORSDS is the average of 12 symptom-specific scores (23). The ORSDS is a valid tool for assessment of opioid side effects after orthopedic surgery, and can be used in clinical trials involving a wide variety of anesthetic and analgesic regimens (23).

Defense & Veterans Pain Rating Scale (DVPRS) and Supplemental Questions (DVPRS-IH, with "IH" indicating "in hospital"): The DVPRS is a graphic tool clinicians can use to facilitate self-reported pain diagnoses from patients. The DVPRS is an easy-to-use pain rating scale where the patient can rate their pain on a scale of 0-10 with 10 being the worst possible pain. The supplemental questions (DVPRS-IH) includes 4 additional questions regarding how pain over the last 24 hours has affected the patient's activity, sleep, mood, and stress. The whole questionnaire takes less than 3 minutes to complete, and will be administered at every preoperative, in-hospital, and follow-up assessment.

Western Ontario and McMaster Universities Osteoarthritis Index Physical Function Subscale (WOMAC-PF):

For patient-reported outcome of function, we will use the data generated by Western Ontario and McMaster Universities Osteoarthritis Index Physical Function Subscale (WOMAC-PF). The entire WOMAC instrument will be administered. This instrument was developed based on patient input and is the instrument of choice to assess outcome post-TKA and THA (20). The WOMAC-PF consists of 17 items related to physical function. Each item is scored on a 5-point Likert-type Scale with descriptors from 0-4 (none, mild, moderate, severe, and extreme difficulty). Scores of each item are summed for a maximum total score on the WOMAC-PF of 68. Higher scores indicate worse functional limitations. Reliability and validity of this instrument have been established (25-27). This will be given before surgery and at Follow-Up Visit 2 after surgery. Licensing rights to this questionnaire have been purchased by the study team for use in this research study.

Falls Questionnaire:

Throughout the study, the patients will be asked about their falls history. The information collected will include but is not limited to, how many falls the patient experienced in the past year (done at baseline), how many falls since the last assessment (in-hospital visits and Follow-Up Visit 2), questions regarding loss of balance, whether or not the patient is afraid of falling, and was medical treatment sought after any falls.

Clinical Assessments

None of the clinical assessments listed below are being done due to safety concerns, as such, if the physical therapist or treating physician feels that due to the patients' medical condition (such as a knee immobilizer), that some or all of the physical therapy tests cannot be completed at the specified protocol time points; the physical therapy testing will be considered optional for these patients and will be done at the discretion of the treating physician and physical therapist. If physical therapy testing is not completed due to the patient preparing for discharge and/or the patient has been discharged, this will not be considered a protocol deviation.

Gait Speed*:* Self-selected gait speed is measured in meters/second while subjects walk a 4 meter path located in the middle of a longer path of 9 meters to avoid acceleration or deceleration. Subjects are asked to walk at their regular pace, and time is measured with a stop watch. This test takes around 2 minutes.

Repeated Chair Stand Test: The repeated chair stand test is a simple test to assess strength of the muscles of the lower extremities and static balance. It measures the time that a person takes to stand from a chair 5 times. It takes approximately 1 minute to complete the repeated chair stand test.

Standing Balance Test:

This test is only performed on those patients who can stand unassisted without the use of a cane or walker. Moreover, the participant stands at an arm's reach of a steady surface on one side *(e.g., bed head/sideboard, grab bar)* and the tester on the other side. There are three (3) balance tests that differ by their feet position (i.e., side-to-side, semi-tandem, and tandem). The balance tests are performed at each assessment visit. For each:

1. The tester will ask the participant if they can stand without the device and are willing to try the test. If they reply "yes" the tester can assist them with getting into the correct position for testing.
2. The tester, for each position, will not only describe to the participant what the test is but will also demonstrate the appropriate position of the feet for testing.
3. The participant will get into the proper position while receiving support from the tester.

When the participant appears to be steady, ask if they are ready. When they reply "yes", the tester says "Ready, begin". The tester begins timing (i.e. starts the stopwatch) once the participant is standing independently without support from the tester. The timing for each test continues until the participant moves their feet, grabs for support, receives support from the tester or the time (10 seconds) has elapsed. This exam takes around 3 minutes.

Single Leg Balance Test:
This test will only be performed in patients who were able to complete the standing balance test. The single leg balance test is recommended to quickly assess global functional level, and its scores are related to risk for falls.

- Participants are asked to stand on one foot for 45 seconds. The other foot is raised so that the raised foot is near but not touching the ankle of their stance limb.
- The participant may use the arms, bend the knee, or move the body to maintain balance.

The tester uses a stopwatch to measure the amount of time the participant is able to stand on one limb. Time commences when the participant raises the foot off the floor. Time ends when the participant either: (1) uses the raised foot (moved it toward or away from the standing limb or touched the floor), (2) moves the weight-bearing foot to maintain his balance (ie, rotated foot on the ground), (3) a maximum of 45 seconds elapses. Three trials are performed in each side and recorded. This exam takes around 6 minutes.

Crude Sensory Examination*:* Sensory examination is carried out by touching lightly the patient in the specified anatomic distribution of L2-L4 and L4-S3 bilaterally, while the patient has his eyes closed. The patient is asked if the sensation is of equal intensity on both sides (normal), or if one side feels less that the other, or is unable to be felt (diminished or absent). This exam takes around 2 minutes.

Hip,Knee and Ankle Range of Motion*:* Range of joint movement is measured with a standard goniometer during passive (movement assisted by the tester) and active (without assistance by the tester) movements. Range of motion is tested with the subject lying in supine on the hospital bed or examination table. This is performed on both sides and recorded in degrees. Range of motion takes approximately 5 minutes.

Straight Leg Raise*:* The subject is asked to raise one lower extremity from the hospital bed up to approximately 45 degrees from the horizontal without bending the knee. The test is performed in both sides, and is recorded as "Yes" if the subject is able to raise the lower extremity higher than 20 degrees from the horizontal, or "No" if unable to lift the leg at that level. During this test the examiner also observes the presence of a knee extension lag, which is defined as a knee flexion (lag) equal or greater than 5 degrees during the straight leg raise. It takes approximately 3 minutes for the straight leg raise activity.

Stair climbing time*:* This test measures the time the subject takes to go up a flight of stairs. Subjects are instructed to use the handrail for safety purposes. The tester uses a stop watch to record time. It takes approximately 5 minutes for this test.

Functional Independence Measure (FIM): The Functional Independence Measurement (FIM) is an outcome measurement tool to assess overall independence during specific functional tasks. The FIM is composed of 18 specific tasks that are commonly assessed and treated by physical therapists, occupational therapists, nurses, and other rehabilitation professionals. FIM tasks related to transfers, walking, and stair climbing ability are all assessed in this study. Each item is scored from 1-7 based on level of independence, where 1 represents total dependence and 7 indicates complete independence. The FIM scale is used to measure the patient's progress and assess rehabilitation outcomes. It takes approximately 15 minutes for the physical therapist to administer the tests for each patient.

4.4 Data Collection

Primary Outcome – Pain

Pain **-** Pain will be measured by the Short-Form McGill Pain Questionnaire (36). (SF-MPQ, version 2) and the Defense and Veterans Pain Rating Scale (DVPRS, which entails a 0-10 numeric rating scale along with step-function visual cues, color-coded visual cues, and verbal descriptors of pain intensity). The specific aim is the 24-hour pain severity as measured by the SF-MPQ. The DVPRS will be used to assess (i) "rebound pain" for pain with movement, compared with baseline, during and after nerve block analgesic effects are experienced and (ii) "block duration" (11) for time interval between block placement and peak postoperative DVPRS score with movement.

Exploratory Outcomes – Physical Function, Other Symptoms, and Recovery from Anesthesia

Data will be recorded by the research coordinator and/or VAPHS Staff Physical Therapists and/or "without compensation" (WOC) physical therapists hired through the University of Pittsburgh specifically for the care of study patients.

Data Management System

Data management will be coordinated at VAPHS by StatCore. Data entry will be primarily performed using the VA's REDCap software (https://vhacdwweb05.vha.med.va.gov/redcap_v6.0.27/index.php?pid=1440) via laptop or desktop personal computers. Data will never reside on the data collection devices, which serve only as portals to the password protected database. Only authorized members of the study team will have access. Data will reside on the VA Informatics & Computing Infrastructure (VINCI) server – which is also password protected and independent from all other servers. Data will be downloaded from the REDCap server by StatCore for analytic and data management purposes. Downloaded data will reside on a password-protected VAPHS secure shared drive. REDCap is a secure web-based platform that can only be accessed through the VA intranet, and it is situated behind the VA firewall. Account login information is required, and then the data are stored on the REDCap server. The data to be entered (and catalogued in a detailed data dictionary) are password-protected within REDCap via login requirements, and the downloaded data are secured by permission only access to the shared drive (\\vhapthshare\Nerve_Block_Study\).

Data collection forms have been designed as paper documents (in Microsoft Word) to allow the full research team to collaborate on content; these paper documents are also being submitted to regulatory (IRB, FDA) and sponsoring (DoD) entities. If modifications to the data collection forms are required, StatCore will maintain versioning control (for both paper versions and the REDCap versions) so that new form versions will be released with prior announcement, a clear and dated history of changes will be maintained, and the final dataset will contain compatible data for analysis.

Across all data collection forms, point-of-entry data checks will be developed to ensure complete and accurate data, ensuring appropriate data precision, guarding against missing or out-of-range data, and prompting for correction of illogical data (e.g. post-surgical procedures dated prior to surgery date). Branching logic will be used as is feasible to ensure that only relevant questions are presented (e.g. if the question "Ever smoked cigarettes?" is answered "No", subsequent questions about smoking history are skipped). The system maintains a full audit trail, identifying each change to the entered data both by date/time and person, and recording both prior and current values, to ensure recovery of inadvertently changed data. It also provides user roles that define read, write, change, and delete privileges on an individual data collection form basis.

Documentation
Working with the study PIs and coordinators, the Clinical Trial Center and StatCore will finalize a Manual of Operating Procedures (MOP, currently in draft phase) to standardize all procedures and staff training in areas such as patient recruitment, measurement, and assessment, as well as data entry, management, and security.
A comprehensive data dictionary and code book has been created during study startup, and will be maintained throughout the study, logging any data field changes or coding changes. This dictionary will identify and characterize all fields available for analysis, and will provide a useful reference document for continuing analysis of the study data. We anticipate that the final versions of the MOP and data dictionary will be available for regulatory or related reviews approximately 12-15 months after study inception.

Confidentiality and Identifiers
All study subjects will be assigned unique study identifiers that will be used to identify all data stored within the data management system. The identifiers will contain no names, social security numbers, or medical record numbers. Patient contact information will be maintained by the study coordinator in locked files separate from the research data. No personal information concerning study participants will be released without participants' written consent, and participants will not be identified by name in any publication of research results.

5.0 Statistical Analysis

5.1 Analysis Plan
Data will first be assessed for outliers (+/- 2 SD from the mean) and normality. Outliers will be corrected, if possible, or dropped from the analyses. Distribution, measures of central tendency, variability, and normality will be examined. Data transformations or non-parametric techniques will be applied as needed. We will delete observations with missing values. Spearman correlation coefficients will be computed to examine associations between nerve block drug treatments, replacement surgery

type (hip versus knee), and the outcome measures (SF-MPQ, SF-8, SF- 36, WOMAC, FIM, repeated chair stand test, Opioid Symptom Distress Scale, Defense and Veterans Pain Rating Scale and its Supplemental Questions) from all time points (1 day, 2 day, 3 day, 4 day, Follow-Up Visit 1, Follow-Up Visit 2). Associations between the outcomes across time points will also be examined with Pearson (SF-MPQ, SF-8, SF-36, WOMAC, repeated chair stand test, Opioid Symptom Distress Scale) and Spearman (FIM, Defense and Veterans Pain Rating Scale and its Supplemental Questions) correlation coefficients. We will test all hypotheses and aims by conducting longitudinal multi-level modeling. The level-one unit will be the repeated measures across time, the level-two unit will be the individual patient, and the level-three unit will be nerve block type and surgical site (knee versus hip) groupings (with additional analyses involving age and diabetes status, reflecting the randomization strata). This mixed model procedure will allow the assessment of outcome and exposure variables relationships while adjusting for covariates, and separate assessments of fixed and random effects (i.e., group and individual-level data) using highly correlated repeated measures data. Covariates included in modeling will be age, diabetes status, gender, weight, smoking status, initial health status (e.g., baseline SF-8 / SF-36 and WOMAC), and concurrent general health status (e.g., daily SF-8, subsequent SF-36, and WOMAC).

The **primary hypothesis** of an improvement in pain (measured by the SF-MPQ- version 2) 24 hr after surgery during in-hospital recovery comparing plain local anesthetics versus ISOC MMPNA will be tested using a mixed model. This procedure will test for nerve block drug treatment and surgical site (hip versus knee) effects, as well as an interaction between them. Differences in pain levels will also be examined across the study's day-of surgery, 1, 2, 3, and 4 day, and Follow-Up Visit 1 and Follow-Up Visit 2 time points. The secondary aims of short- and long-term physical therapy and rehabilitation-related benefits will also be examined for nerve block drug treatment and surgical site by a mixed model. The tertiary aim to determine differences in opioid-related side effects will use a mixed model. As with other analyses, there will be an examination for nerve block drug treatment and surgical site effects, as well as an interaction between them, along with analyses of the other randomization strata (age, diabetes) as described above.

The **exploratory aims** of physical therapy progress, return-to-home benefits, etc. will be examined using a mixed model. This procedure will test for nerve block type and surgical site effects, as well as an interaction between them. Number of days from the joint replacement procedure to the patient's home discharge will be assessed. Pain responses, as measured by the SF-MPQ – version 2, and use of postoperative opioids with additional measurement by the Opioid-Related Symptom Distress Scale will also be assessed. General health status will be evaluated with the SF-8 and SF-36. Measures of pain, analgesic side-effects, and general health status will be covariates included in the modeling of the effect of MMPNA on return-to-home.

Only after all data are analyzed and results are checked and verified by the biostatisticians will the study be unblinded.

5.2 Adverse Events. For adverse events, we will calculate cumulative probability using survival analysis techniques such as the product-limit estimator. Unlike proportions, product-limit estimators can be applied at various times following randomization, and can take into account when adverse events occur. The six-week incidence (and 95% CI) of individual adverse events by organ system and relatedness to the study will be calculated for each group. We will estimate the incidence of adverse

events in both groups with specific focus on those deemed definitely, probably, or possibly related to interventions. For adverse events, clinical judgments will be considered more important than statistical testing.

Prolonged analgesic duration Sustained / prolonged nerve block analgesia, which we hypothesize to be true in our ISOC MMPNA Group, is NOT a complication that warrants medical attention as a possible complication. That this is NOT a complication is especially true in the context of perineural analgesia being designed to facilitate postoperative physical therapy in the first few days after surgery. In our evaluation of analgesic duration, a central question for patients will be "when did you first take a prescription opioid pain pill, but it did not help?" Another (indicating even further pain severity) is "when did you first get an intravenous opioid dose, but it did not help? The dates and times of these events are important and clinically practical indicators that the perineural analgesia is no longer effective. This is because postoperative ***oral*** multimodal analgesia is designed to (i) supplement the lingering analgesic effects of the nerve block, and (ii) delay the onset of the peak pain score encountered after the perineural analgesia "wears off." "Peak rebound pain scores" may not necessarily entail excruciating pain. But if excruciating pain is encountered despite oral and intravenous opioids, then it is likely that there is no persisting perineural analgesia. Conceptually, when combining CBD with bupivacaine (in the ISOC MMPNA group), the bupivacaine provides short-lived numbness and analgesia (e.g., a theoretical 12-16 hr), but the CBD likely sustains perineural analgesia without numbness (e.g., for an additional theoretical 24 hr). The study is designed to accurately capture these two separate phases of analgesia, since we do not have preliminary data on these separate phenomena (analgesia with numbness, then analgesia without numbness).

Prolonged numbness in the distribution of the nerve blocks If a patient encounters ***numbness and weakness*** for an extended period of time after a nerve block is given, then certainly serious consideration is given to the possibility of nerve damage from surgery, nerve block, other factors, or a combination of these. We do not have any preliminary data indicating the duration of numbness as a separate entity from the duration of analgesia. In our preliminary data (published), the analgesic duration (with or without numbness) upper bound of the 95% confidence interval is 49 hr. By definition, the 95% interval (30-49 hr) is the interval representing that we are confident that the mean lies within this interval 95% of the time. So with the conservative 48 or 49 hr "upper bound" as the possible mean, and with a standard deviation of analgesic duration being 14 hr, we will apply a "mean and standard deviation" principle of "nerve damage" possibility. If the mean is 48 hr, and the standard deviation is 14 hr, then 97.5% of these nerve blocks' numbness will dissipate by 76 hr (i.e., mean plus 2 standard deviations). For simplicity, if any patient has numbness (i.e., ***both analgesia and numbness***, but *not analgesia without numbness*), beyond 72-76 hr after injection, then the participant will be referred (presumably while still in the hospital) to the Physical Medicine and Rehabilitation Service for initial evaluation, with subsequent referral to neurosurgery if deemed appropriate based on electromyography (EMG), imaging, or other workup. If minor symptoms of paresthesiae with pain and/or weakness persist over time, patients will be similarly referred to the Physical Medicine and Rehabilitation Service for outpatient workup, and these events will be recorded in study logs.

ISOC MMPNA Nerve Blocks From July 1, 2011 until December 31, 2014, there were a total of 1830 patient-block encounters involving our ISOC MMPNA program, entailing the routine use of 3-4 drugs in peripheral nerve blocks. At our institution, the incidence of EMG-documented nerve damage

attributable to the precise needle location of the block was 2/1830 (0.11%), and attributable to the precise or approximate needle location of the block was 4/1830 (0.22%). Additionally, there were 2 cases (0.11%) of postoperative EMG findings that could neither rule out nor confirm nerve damage attributable to the needle location of the block. There were also 6 cases of postoperative EMGs performed where the original suspicion of block-related nerve damage was indeed negative per EMG. Therefore, of 12 EMGs ordered, 6-8 were unable to localize nerve damage to the needle injection site. There were, separately reviewed, 7 cases of abnormal postoperative physical exam findings that were judged to be "possibly block related," for which there was no EMG ordered to appropriately evaluate. Based on the proportions described above, we will assume that if these 7 had EMGs ordered, 3 may have proven to be positive. Therefore, in our conservative estimation, the risk of nerve damage that has been (or may be) traceable to the site of nerve block injection is 9/1830, or 0.5%. The 95% confidence interval of this incidence is 0.24% to 0.97%. In literature review, the risk of nerve damage from hip replacement ranges from 0.2% to 8% (Zappe 2014, Arch Orthop Trauma Surg 134:1477-1482). Our 95% confidence interval of the incidence of EMG-documented nerve damage (0.24% - 0.97%) lies precisely at the low end of this range. Meanwhile, contemporary estimates of risk of peripheral nerve block (PNB) anesthesia have been cited as follows. For common PNB techniques entailing the use of plain local anesthetics, the rate of neuropathy after interscalene brachial plexus block, axillary brachial plexus block, and femoral nerve block is reported as 2.84% (95% CI 1.33-5.98%), 1.48% (95% CI: 0.52-4.11%), and 0.34% (95% CI: 0.04-2.81%), respectively, based on detailed review of prospective randomized studies-to-date (as of 2007; n=10,309; Brull 2007, Anesth Analg 104:965-974). In another single-institution study of 1010 consecutive peripheral nerve blocks with plain local anesthetics, new, all-cause, neurological symptoms were present in 56/690 blocks (8.2%; 95% CI: 6.8-10.2%) at day 10, 37/1010 (3.7%; 95% CI: 2.7-5.0%) at 1 month, and 6/1010 (0.6%; 95% CI: 0.27-1.3%) at 6 months (Fredrickson 2009, Anaesthesia 64:836-844). Most symptoms (Fredrickson study) were due to causes unrelated to the block: 4 of 1010 were ultimately unrelated to the block, but for the other 2:1010 (0.2%), attribution to the block could not be ruled out. Based on the literature review described above, our 95% CI of 0.24%-0.97% for long-term complications (traced by EMG to the nerve block injection site) associated with our ISOC MMPNA (the 4-drug single-injection nerve blocks) falls within the 95% CI of published studies (lower bound of the 95% confidence interval being as low as 0.04%, and upper bound of the 95% confidence interval being as high as 5.98%) for nerve blocks using solely local anesthetics without other perineural adjuvants. We have no evidence to indicate that our ISOC MMPNA use is unsafe in the context of standard rates of complications when using plain local anesthetics, or in the context of undergoing surgery.

5.3 Incidental Findings.

All instances of incidental findings considered to be clinically significant will be addressed in the following manner: the PI will determine whether a finding is significant to warrant further action. If the PI determines the finding is serious enough to be labeled an adverse event; then the issue will be addressed with the patient's primary care physician or another specialist. If the finding is not a serious event, then it will be listed as 'incidental' and no further action will be taken.

NOTE: The study team will capture the study data using CRFs that have been created by the study team. All hard copy documents will be protected and stored using generally-accepted measures for research confidentiality.

5.4 Interim Analysis.

During the course of a clinical trial, there is an ethical mandate to monitor the progress of the trial with interim analyses to ensure patient safety. A number of group sequential methods have been developed which permit comparisons to be made, while maintaining an overall type I error rate. The investigators will work with the Data and Safety Monitoring Board to select an interim monitoring approach. It is likely that an approach which adjusts the type I error rate in a non-uniform fashion, so that the majority of the type I error is conserved for the final treatment comparison. Thus, a large difference would be needed early in the trial to find a significant difference. Statistical significance parameters will be appropriately adjusted to account for these multiple interim analyses. At his time, the interim analyses are projected to occur (separately for TKA and for THA) at 5/20 patients and at 10/40 patients. If at these points the specific aims have been met (for the ISOC MMPNA treatment), then the Data Safety Monitoring Board will be charged with the decision to terminate the study.

5.5 Dissemination of Results.

The whole research team will engage in the interpretation of the study results. VAPHS will be able to disseminate the research results through email newsletters to their providers. The team will be able to present the research findings at regional provider meetings and major professional conferences including: American Society of Anesthesiologists, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopedic Surgeons, American Physical Therapy Association, and American College of Rheumatology. The findings will be published in peer reviewed journals with appropriate access to the end user.

5.6 Sample Size Determination

Although the SF-MPQ data is the basis of our specific aim, we do not have our own preliminary SF-MPQ data. So we will base our sample size on our most robust data, that being nerve block duration from our observational data (40 hr mean, with 14 hr standard deviation). Hip replacement and knee replacement surgery are different procedures requiring anatomically different nerve blocks as described above, so we will consider these samples as separate. We consider a doubling of the nerve block duration (15 hr for plain bupivacaine, 30 hr for bupivacaine-CBD) as a clinically significant difference with respect to the military objectives of evacuation and transport. We forecast that as a single-drug (and based on historical literature), the standard deviation of plain bupivacaine duration would be half of the 15 hr projected duration (i.e., 7.5 hr). Due to likely variability in study participant responsiveness to the 4-drug mixture, we predict that the standard deviation of the bupivacaine-CBD treatment would also be half of the projected 30 hr duration (i.e., 15 hr). We believe that the 30 (SD=15) hr duration for bupivacaine-CBD is a reasonably conservative duration based on our preliminary data of 40 (14) hr block duration. Using a 2-tailed t-test with α=0.05, 20 patients per procedure for bupivacaine treatment, and 80 patients per bupivacaine-CBD treatment would yield 95% statistical power. This sample size will also accommodate for our multiple secondary aims. Attrition of 6 active control treatment patients (n=14) and of 24 MMPNA-treated patients (n=56) will still yield just over 80% statistical power. All calculations were performed using IBM SPSS SamplePower version 3.0.1, Chicago, IL.

6.0 Subject Population

6.1 General Characteristics

This study will enroll veterans undergoing a total knee or hip replacement, no older than age 85.

6.2 Vulnerable Subjects and Special Populations
Vulnerable subjects will not be enrolled into this research study.

6.3 Incompetent Subjects
Incompetent subjects will not be enrolled into this research study.

6.4 Inclusion/Exclusion Criteria

Inclusion Criteria:
Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Age between 18 and 85, and undergoing a total knee or hip replacement.
2. Fluent in English, decision competent, willing and able to provide written informed consent, and able to complete the study's schedule of assessments.
3. Able to walk >3m without an assisting device.
4. Have a BMI ≤ 40 kg/m^2.

Exclusion Criteria:
Subjects who meet *any* of the following exclusion criteria will not be enrolled in this study.

1. Current participation in another orthopedic/PT/rehab/anesthesiology interventional clinical trial.
2. Are at significant behavioral risks or have refractory major psychiatric disorders.
3. Revision surgery on the same extremity.
4. Have an ASA Physical Status classification of 4 or higher.
5. Have been diagnosed with clinically significant neuropathy with its origins in either diabetes or other causes; have neuromuscular disease that would influence data collection.
6. Have a surgically-fused lumbar spine, or a spinal cord simulator, or other condition that would contraindicate or prohibit the conduct of spinal anesthesia.
7. At significant risk for postoperative substance abuse, or immediate-postoperative substance abuse withdrawal symptoms (alcohol, cocaine, enrolled in methadone or buprenorphine opioid withdrawal programs, etc.). Previous or current use of marijuana will not be an exclusion for study enrollment.
8. Are undergoing TKA/THA for a tumor.
9. Have contraindications (e.g., anaphylaxis) to any of the study drugs.
10. Have a systemic fungal infection.
11. Have a known hypersensitivity to bupivacaine hydrochloride or to any local anesthetic of the amide-type or to other components of bupivacaine hydrochloride solutions.
12. Have a known or suspected buprenorphine hypersensitivity (not including nausea and/or vomiting).
13. Have a GI obstruction.
14. Have paralytic ileus.
15. Pregnant women
16. Have had a kidney or liver transplant.

Veteran subjects will not be excluded from participation based on smoking status, diagnosis of obstructive sleep apnea, or baseline monitored consumption of therapeutic opioids for documented

medical indications; instead, these variables will be codified and quantified for subsequent covariate statistical analysis. Prior to study enrollment, the principal investigator has the final decision regarding patient eligibility.

Pregnancy is an exclusion criterion for surgery and is checked by the clinical team. The Research team will confirm that the pregnancy test has been done (where applicable).

6.5 Recruitment Procedures

The study team (typically the coordinator) will prescreen patients from both the orthopedic and IMPACT clinics. If the coordinator finds a patient that may be eligible, the coordinator will contact a member of the patient's clinical care team (orthopedics/surgical team or IMPACT clinic team). The patient will then be approached by a member of their clinical care team to see if they are interested in participating in research opportunities. If the patient expresses interest and agrees to be contacted by the study team, the study team will be notified via a phone call or encrypted email. Once notified, the study team will either provide the patient with the ICF to take home and review or will call the patient and send the consent form in the mail for them to review. The study team will let the patient know that s/he can call at any time with questions to help aid in the decision, and that the study team will be calling the patient in a few days after s/he has had time to review the ICF, and/or to declare interest and/or ask questions. If the patient is interested, the study team will schedule the potential participant for their screening/baseline visit, at which time ICF completion will occur.

If the patient is scheduled for an eConsult IMPACT clinic visit, the study team will schedule the patient to come in for a research only visit to complete the screening/baseline visit. If the patient is already scheduled for a face-to-face IMPACT clinic visit, the study team will ask the patient if they wish to complete the screening/baseline visit on the same day or would they prefer to schedule a separate visit, since the estimated research visit is expected to take approximately three (3) hours. The consent process will occur in an empty room, or, if the potential participant is not ambulatory, the curtain will be drawn and the discussion will be kept quiet to ensure patient confidentiality. The patient may take time to review this with family. One of the physician-investigators- will make final determination of eligibility of subjects. A subject can sign the consent form, but after physician review, the potential participant may be declared ineligible.

6.6 Informed Consent

Prior to any study procedures being performed, each patient must sign the informed consent form and HIPAA form (pending HIPAA waiver applications), this includes any screening procedures. Only English speaking subjects will be enrolled into this study.

7.0 Risks/Benefits

7.1 Potential Risks

Risks of Physical Therapy Testing

The risks associated with the battery of physical tests do not in our estimation differ from those used in our ISOC. General risks may include temporary muscle soreness (common: 10 to 25 out of 100 people), an exacerbation of knee/hip pain and inflammation (rare: less than 1 out of 100 people), or tripping and falling during testing (rare: less than 1 out of 100 people). During testing, risks of tripping and falling

will be minimized by our team providing direct stand-by supervision with trained testers. Signs and symptoms of knee/hip inflammation will be monitored before and after each testing visit. If knee inflammation occurs, subjects will be referred to their physician for evaluation. Because subjects will participate in physical tests, there is a rare risk (less than 1 out of 100 people) that they may experience chest pain, dizziness, shortness of breath, heart attack, or stroke. To minimize this risk, we will follow the recommendations from the American College of Sports Medicine and American Heart Association (ACSM/AHA) guidelines for physical testing. As with any experimental procedure, there may be adverse events or side effects that are currently unknown, and some of these unknown risks could be permanent, severe or life-threatening.

Risks of Anesthesia and/or Physical Therapy

Likely- occurs in more than 25% of people (more than 25 out of 100 people): None listed above and beyond those listed in the consent forms for surgery and anesthesia, and/or consistent with standard of care for surgery, anesthesia, and physical therapy at our institution.

Common – occurs in 1% to 25% of people (1 to 25 out of 100 people): the possibility of subjects in the Active Control group temporarily requiring more oral analgesics than subjects assigned to the ISOC MMPNA treatment group. Otherwise, none listed above and beyond those listed in the consent forms for surgery and anesthesia, and/or consistent with standard of care at our institution.

Rare – occurs in less than 1% of people (less than 1 out of 100 people). Regarding goniometry testing: possible pain or strain of the knee. Regarding the nerve block: bleeding, infection, and/or nerve damage. Otherwise, none listed above and beyond those listed in the consent forms for surgery and anesthesia, and/or consistent with our ISOC.

Data Security

All case report forms (CRF) will remain on-site at VAPHS, and REDCap data will remain behind the VA firewall on the VINCI server. Any paper CRFs will be kept in a locked cabinet in the study coordinator's locked office at VAPHS, University Drive Division. Only authorized members of the study team will be allowed to access the study documents (hard-copy or automated). All electronic medical record data within the standard of care will be stored on CPRS within the VAPHS network, while all de-identified study-specific data is stored securely on the VINCI server, as previously described.

Any loss or compromise of any VA sensitive information (including research data), VA equipment or device, or any non-VA equipment or device that is used to transport, access, or store VA information will be reported in accordance with the reporting requirements outlined in VA Handbook 6500.

All research records will be maintained in accordance with the Veterans Health Administration (VHA) Records Control Schedule. Paper records will be disposed of using methods deemed appropriate by the VAPHS Privacy Officer, and all electronic data will be sanitized using methods rendered appropriate by the VAPHS ISO.

7.2 Potential Benefits:

Subjects will receive no apparent direct benefit from their participation in this research study. The information obtained from this study may lead to our recommending specific pain management techniques to allow a more prompt return to normal activities of daily living and a better outcome from physical therapy.

7.3 Alternative Procedures**:**
If potential subjects decide not to participate in this research study, they will undergo TKA/THA surgery and be offered the routine choices of anesthetic currently offered to our patients undergoing the same procedure. The same spinal and MMPNA nerve block techniques are used as our ISOC. For TKA patients that have spine-specific contraindications, there are other ISOC nerve block techniques used (e.g., the psoas compartment lumbar plexus and sciatic nerve blocks for surgical anesthesia and postoperative analgesia, or "lum-sci" for short). It is conceivable that TKA patients (opting not to participate in the study) without spine abnormalities may be offered a lum-sci as part of ISOC. However, this lum-sci block leads to a more profound postoperative numbness that can preclude the study-specific physical therapy protocol from reliably commencing on the morning of postoperative day 1. THA routinely involves spinal anesthesia (and the described ISOC MMPNA blocks) if there are no contraindications (to the spinal such as previous spine fusion or spinal cord stimulator), depending on the clinical situation and other health status factors. Local anesthetics used for our routine nerve blocks (i.e., bupivacaine, for patients not participating in the study) are the same as those used in the study (both ISOC MMPNA and Active Control). In our ISOC, nerve block patients receive all 4 drugs in the nerve blocks (the local anesthetic and the 3 other CBD drugs), even though we do not know (by formal study) if the 4-drug nerve block gives longer-acting pain relief, or longer-acting unwanted numbness, than does the nerve block with use of only the local anesthetic. Patients may have a history of allergy to Novocain®; our nerve blocks do not use Novocain itself, and so the risk of allergy from other local anesthetics that we use for patients is exceedingly rare. Many medical centers performing TKA/THA surgery do not routinely offer patients a choice in anesthesia technique, and most medical centers do not offer nerve blocks of any kind for TKA/THA surgery. However, MMPNA nerve blocks are the ISOC at VAPHS, and the anesthesia doctors who perform these nerve blocks here are very well-experienced.

7.4 Costs and Payments
Subjects will not be required to pay for any services outside of the VHA that may be required as part of participating in this research study.

Patients will be compensated $20.00 for completing the pre-surgery questionnaires and physical therapy tests, $20.00 total for the tests completed while the patient is in the hospital and then $60.00 when they complete the study tests at follow-up visit 2 after their surgery (Possible total per patient of $100.00 if they complete all study visits).

8.0 Data Safety Monitoring

External DSMB
An external DSMB (through the Clinical and Translational Science Institute (CTSI) at the University of Pittsburgh) will review the progress of the study and perform interim reviews of safety data in order to protect subject welfare and preserve study integrity. Termination or modification may be recommended for any perceived safety concern based on clinical judgment,

including but not limited to a higher than anticipated rate for any component of the primary endpoint resulting in adverse events, or unexpected SAEs.

An initial meeting of the DSMB will be held prior to any subject enrollment in the study in order for the members to review the charter, to form an understanding of the protocol and definitions being used, to establish a meeting schedule, and to review the study modification and/or termination guidelines. Subsequent interim and final review meetings will be held to review and discuss interim and final study data (adverse events, protocol deviations, enrollment summary and tables for overall primary and secondary endpoints). Frequency of meetings will be every six months, unless the board determines otherwise.

Local DSMB

Locally, a data and safety monitoring plan will be implemented to ensure that there are no changes in the benefit/risk ratio during the study and that confidentiality of research data is maintained. It will meet as needed to discuss the study (e.g., study goals, progress, modifications, documentation, recruitment, retention, data analysis and confidentiality) and address any issues or concerns. The principal investigator, clinical coordinator and research staff, will take part in these discussions. These will occur on an as needed basis but at least twice a year. Any instances of adverse events, protocol deviations, or other problems identified during the discussions will be reported as soon as possible within the required reporting timeframes using the standard forms and/or procedures set forth by the IRB. In addition, clinical coordinators may review study documentation and/or consent forms to ensure that subject's confidentiality is maintained.

9.0 Adverse Event Reporting

9.1 Adverse event definitions

Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Adverse reaction means any adverse event caused by a drug.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction"

- *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site PI) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Serious, suspected adverse reaction. A suspected adverse reaction is considered "serious" if, in the view of the Investigator (i.e., the study site PI) or Sponsor, it results in any of the following outcomes: death, a

life-threatening adverse reaction, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

- Important drug-related medical events that may not result in death, be life-threatening, or require hospitalization may be considered "serious" when, based upon appropriate medical judgment, they may jeopardize the research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected, suspected adverse reaction. A suspected adverse reaction is considered "unexpected" if it is not listed in the general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

9.2 Recording/Reporting requirements

Eliciting adverse event information
Research subjects will be routinely questioned about adverse events throughout their hospital stay and at study visits.

Recording requirements
All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

Adverse events or abnormal test findings felt to be associated with the study drug(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

Abnormal test findings
An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
    - Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the Sponsor-Investigator of the IND application

Causality and severity assessment

The Sponsor-Investigator of the IND application will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s); and 3) if the adverse event meets the criteria for a *serious adverse event*.

If the Sponsor-Investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s)", the adverse event will be classified as *associated with the use of the study drug(s)* for reporting purposes. If the Sponsor-Investigator's final determination of causality is "unknown but not related to the study drug(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

9.3 Reporting of adverse reactions

Reporting of adverse reactions to the FDA

Written IND Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500 A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a *serious and unexpected, suspected adverse reaction*. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

Telephoned IND Safety Reports – Fatal or life-threatening suspected adverse reactions
In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any *unexpected, fatal or life-threatening suspected adverse reaction.*

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

Reporting adverse events to the responsible IRB
In accordance with applicable policies of the VAPHS Institutional Review Board and the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s)*; 2) *fatal or life-threatening*; and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

Reporting adverse events to the Independent Research Monitor
The Independent Research Monitor for this research study is Michael Mangione, MD. The Research Monitor shall be responsible for evaluating any risks or concerns of the research and to report findings to the IRB. The Independent Research Monitor will have the authority to stop this research protocol, remove individual human subjects from the research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. The research monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the research monitor must comment on the outcomes of the event or problem and in case of a serious adverse event or death, comment on the relationship to participation in the study. The research monitor must also indicate whether he concurs with the details of the report provided by the principal investigator. Reports for events determined by either the investigator or research monitor to be possibly or definitely related to participation and reports of events resulting in death must be promptly forwarded to the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO)

As the research monitor for this study, Dr. Mangione will be responsible for the following duties per his discretion and/or as required:

- Reviewing monitoring plans and IDSMB reports
- Overseeing study interventions and interactions
- Observing recruitment and enrollment procedures, including the consent process
- Overseeing data collection and analysis
- Review of SAEs and unanticipated problems

Reporting adverse events to USAMRMC ORP HRPO

The following post-approval submissions must be reported to the USAMRMC ORP HRPO:

a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change in the IRB of Record, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.

b. A copy of the IRB continuing review approval letter and continuing review report must be submitted to the HRPO as soon as possible after receipt of approval.

c. The final study report submitted to the IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

d. The following study events must be promptly reported to the HRPO by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil<Caution-mailto:usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil>), or by facsimile (301-619-7803) or mail to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

(1) All unanticipated problems involving risk to subjects or others.

(2) Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the sponsor, or regulatory agencies.

(3) Any instances of serious or continuing noncompliance with the federal regulations or IRB requirements.

(4) The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research.

(5) The issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any government regulatory agencies.

(6) Change in subject status when a previously enrolled human subject becomes a prisoner must be promptly reported to the USAMRMC ORP HRPO. The report must include actions taken by the institution and the IRB.

e. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

Withdrawal of subjects due to adverse events

The study drug is administered only once, at the time of the nerve block before surgery. So no adverse event would involve "continuous receipt of study drugs."

We do not anticipate any withdrawn participants from the study, with the exception of those for which the anesthetic care plan was converted to GETA. This is because (i) the nerve blocks and/or spinal failed, or (ii) that the nerve blocks and/or spinal were appropriate for the "typical" surgical procedure. In further detail, the particular surgical procedure that was forced to a GETA anesthetic plan was likely atypically lengthy or complex, rendering the study case as likely not comparable to other enrolled/completed study participants. Therefore, we do not anticipate any further data collection as being representative of a scientifically meaningful "intent-to-treat."

The basis of adverse event severity related to the study entails 1) association with the investigational drug or study treatment(s); 2) serious nature of the adverse event; and 3) unexpected nature of the adverse event. The nerve block drug involved in the active control group (bupivacaine) to which the experimental group drugs are added (clonidine-buprenorphine-dexamethasone) are not expected to create untoward surgical events and/or blood loss complications since none of these drugs alter physiologic coagulation. It is not anticipated that surgical complications that entail blood loss, of whatever severity, will be traceable to the nerve block treatment group. However, we will still record and grade estimated blood loss of the surgical procedure (<500 mL, 500-1L, > 1L) and determine any potential associations with nerve block treatment group.

Subjects withdrawn from study participation due to an adverse event will be replaced.

10.0 Resources

The following VAPHS resources will be utilized: Investigational Drug Service (IDS), Clinical Trials Center (CTC) and the Surgery and Medical Service Lines. StatCore and IDS will be used for randomization and the receipt, accountability, storage, preparation and dispensing of the study drugs, respectively. The CTC will handle all regulatory and study coordinator activities. The Surgery Service Line will be enlisted for preoperative (IMPACT Clinic), anesthesiology, and orthopedic resources, and the Medicine Service Line will be used for physical therapy resources.

11.0 Collaborations

The statistical analysis for this research study will be done in collaboration by VAPHS StatCore. Physical therapy testing at VAPHS will be conducted in conjunction with University of Pittsburgh-hired physical therapists in order to provide study-specific physical therapy coverage on weekends and/or after hours on weekdays.

12.0 Qualifications of the Investigators

Brian A. Williams, MD, MBA: Dr. Williams is a full-time VA employee, and is currently the Director of Ambulatory Anesthesiology and Acute Pain Medicine Service/Regional Anesthesia at the VA Pittsburgh Healthcare System. He is also a Professor in the Department of Anesthesiology at the University of Pittsburgh as well as their director of ambulatory anesthesia. He has over 80 publications in his field and has been doing research for over 20 years.

Sara R. Piva, PhD, PT: Dr. Piva is an Associate Professor in the Department of Physical Therapy, School of Health and Rehabilitation Sciences, University of Pittsburgh. She is also the Co-Director of the Physical Therapy- Clinical and Translational Research Center (PT-CTRC), funded by the Clinical and Translational Science Institute- NIH. Her research focuses on musculoskeletal rehabilitation to improve functional outcome in patients with arthritis. She has participated in several clinical trials of exercise in arthritis and has received funding from NIH, PCORI, and several research foundations and national professional associations. Dr. Piva has been published in over 40 peer reviewed papers on rehabilitation topics.

Peter Z. Cohen, MD: Dr. Cohen has been practicing medicine for 51 years. Dr. Cohen graduated from the University of Pittsburgh School of Medicine in 1963. Dr. Cohen specializes in Orthopaedic Surgery and is the Chief of Orthopaedic Surgery at the VA Pittsburgh Healthcare System.

James W. Ibinson, MD, PhD: Dr. Ibinson is an Assistant Professor of Anesthesiology at the University of Pittsburgh. He is currently active in research, and the chief focus of his research is functional magnetic resonance imaging of pain processing, regional anesthesia, and acute pain management. He is one of six total anesthesiologist team members on the VAPHS Acute Pain Medicine Service / Block Team.

Catalin S. Ezaru, MD, and Marsha Ritter-Jones, MD, PhD: Drs. Ezaru and Ritter-Jones are both Assistant Professor of Anesthesiology at the University of Pittsburgh.

Visala Muluk, MD: Dr. Muluk is the Director of the IMPACT clinic at VAPHS and has taken part in various research studies at VAPHS.

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APPENDIX 1: Study Calendar

	Screening Visit[a]	Baseline Visit	Day of surgery		Post-Op Day 1	Post-Op Day 2	Post-Op Day 3	Post-Op Day 4	Post-Op Day 5	Follow-Up Visit 1[d]	Follow-Up Visit 2[c, e]
			Pre-Procedure	Post-Procedure							
Clinical Assessments											
Informed Consent	X										
Determine Eligibility	X										
Demographics	X										
Orthopedic & IMPACT evaluation		X									
Crude Sensation in L2-L4 & L4-S3		X			X	X	X	X	X		X
Straight Leg Raise & Range of Motion		X			X	X	X	X	X		X
Functional Independent Measure (FIM)		X			X	X	X	X	X		X
Standing Balance Test		X			X	X	X	X	X		X
Single Leg Balance Test[g]		X									X
Gait Speed		X			X	X	X	X	X		X
Repeated Chair Stand Test		X				X	X	X	X		X
Stair Climbing Time		X									X
Physical Therapy/ Therapeutic Exercises					X	X	X	X	X		
Comorbidity (CIRS)		X									
Interim Changes											X
Discharge Disposition											X
Opioid Consumption							X[g]				
Anesthesia/Study Drugs			X								
Adverse Events		X	X	X	X	X					
Concomitant Medications		X	X	X	X	X					

	Screening Visit	Baseline Visit	Day of surgery		Post-Op Day 1	Post-Op Day 2	Post-Op Day 3	Post-Op Day 4	Post-Op Day 5	Follow-Up Visit 1	Follow-Up Visit 2[c, e]
			Pre-Procedure	Post-procedure							
Questionnaires											
SFMPQ-2[b]		X	X	X	X	X	X	X	X		X
DVPRS		X	X	X						X	X
DVPRS- in hospital[b]					X	X	X	X	X		
ORSDS[b]		X			X	X	X	X	X		
QOR-15[b]		X			X	X	X	X	X		X
WOMAC		X									X
SF-8[b]			X		X	X	X	X	X	X	
SF-36		X									X
Falls Questionnaire		X			X	X	X	X	X		X

a. The screening visit and baseline visit can be completed on the same day.

b. On post-op hospital days and post-op week 6 follow-up visits, these questionnaires will be completed before the subject has their first physical therapy session for the day.

c. If a patient decides to withdraw from the study after having their surgery, or is withdrawn by the study team during or after their surgery, they will be asked to complete Follow-Up Visit 2.

d. Follow-up visit 1 will occur with the patient's already scheduled standard of care follow-up orthopedic visits. Follow-Up Visit 1 may be performed as a phone call if necessary.

e. Follow up visit 2 will be scheduled to coincide with the patient's standard of care follow-up orthopedic visits.

f. Patient must pass the standing balance test first, before the single leg balance test can be attempted.

g. Opioid consumption will stop being collected at the time of the patient's discharge.

APPENDIX 2 – Protocol Amendments

Protocol Version	Approved Date
Original Protocol	February 11, 2016
Amendment 1	February 16, 2016
Amendment 2	April 20, 2016
Amendment 3	August 05, 2016
Amendment 4	September 12, 2016
Amendment 5	March 17, 2017
Amendment 6	June 6, 2017
Amendment 7	July 11, 2017
Amendment 8	November 20, 2017
Amendment 9	

Amendments below are listed beginning with the most recent amendment.

Amendment 9

Protocol Changes:

Change: Clarification in the exclusion criteria that previous or current use of marijuana will not be considered a study exclusion.

Rationale: We are seeing an increase in the use of marijuana in potentially eligible patients. The use of medical marijuana is approved in the state of Pennsylvania and we want to clarify that the use of marijuana will not be considered an exclusion for this research study. We do not feel as if these patients will be at a higher risk for post-operative substance abuse and therefore can be enrolled into the research study.

Change: Addition of previous liver or kidney transplant as an exclusion criterion.

Rationale: These patients are at higher risk for prosthetic joint infection, from the immunosuppressant drugs that they receive as part of their post-transplant care.

Change: Add Dr. Marsha Ritter-Jones as a co-investigator on the protocol.

Rationale: Dr. Ritter-Jones was added to the IRB application and approved as a co-investigator on a previous amendment; however, her name was inadvertently not added to the FDA protocol.

Amendment 8

Protocol Changes:

Change: Clarification that physical therapy testing missed due to the patient preparing for discharge and/or the patient being discharged will not be considered a protocol deviation.

Rationale: The study team has run into several instances when the physical therapist presented to the patient's room to do physical therapy, and have found that the patient has already been discharged or is preparing to leave. As this is not a safety issue, and the study team can't always avoid this situation, the protocol has been modified so that these occurrences will no longer be protocol deviations.

Amendment 7

Protocol Changes:

Change: Clarifications and updates to the recruitment strategy.

Rationale: In order to help boost enrollment, the recruitment strategy has been clarified and adjusted slightly.

Amendment 6

Protocol Changes:

Change: Update the names of the 2 week and 6 week Post-Op Visits to Follow-Up visits 1 and 2 respectively.

Rationale: These visits are scheduled by the ortho clinic and are not always at 2 and 6 weeks. Updating the names of the visits allows for flexibility as the study team does not have control over when ortho schedules these visits.

Change: Add that Follow-Up Visit 1 can be performed as a phone call if necessary.

Rationale: Follow-Up visit 1 is questionnaires only. If the study team is unable to meet with the patient during their ortho schedule Post-op week 2 visit (study Follow-Up visit 1), the study team would like the ability to perform the questionnaires over the phone to complete the visit.

Change: Update the study calendar to reflect that concomitant medications will not be collected after the end of Post-Op Day 2.

Rationale: The study drug is no longer in the patient's system after Post-Op Day 2; therefore, the study team does not feel it is necessary to collect this data after this time point.

Change: Update Footnote "g" in the study calendar to clarify that the study team will stop collecting opioid consumption data at the time of the patient's discharge.

Rationale: This was not clear as previously written.

Change: Adding a statement that physical therapy assessments throughout the study will be considered optional if there is a patient medical condition that prohibits them from performing the assessments, the decision will be at the discretion of the treating physician and/or physical therapist.

Rationale: None of the physical therapy assessments are being done for safety purposes, the physical therapy portion of this study is strictly for data purposes only. After enrolling 22 patients, the study team has run into several instances where some or none of the physical therapy assessments could be done at the specified time points due to patient medical issues (such as a knee immobilizer). To cut down on study team and IRB time in preparing and reviewing these deviations, the study team will consider the physical therapy assessments optional if in the opinion of the treating physician and/or physical therapist the assessments cannot be completed due to a patient medical issue.

Change: Adding MyHealth*e*Vet as a communication tool after the patient has signed consent.

Rationale: MyHealth*e*Vet is a very convenient and secure tool for the patient and study team to use for communication. The addition of using MyHealth*e*Vet will make contacting the study team more convenient for the patient.

Change: Added ankle range of motion to the physical therapy tests being conducted.

Rationale: Study team would like to begin collecting this data to ensure that the patient will be able to walk and perform the other physical therapy tests.

Amendment 5

The overall reason for the amendment: To update the Independent Research Monitor to Michael Mangione, MD and to add that the study team will evaluate patients who have a significant health change after their baseline visit but before their surgery, to determine if the baseline visit should be repeated for data purposes only.

Protocol Changes:

Change: Replace Dr. Ezaru as the Independent Research Monitor with Dr. Michael Mangione.

Rationale: The Independent Research Monitor is being updated to add Dr. Ezaru as a study co-investigator as he is also able to perform the study-specific nerve blocks and assist with other study matters, making him a valuable addition to the study team.

Change: Add Dr. Hulimangala Rakesh as a co-investigator on the protocol.

Rationale: Dr. Rakesh was added to the IRB application and approved as a co-investigator on the previous amendment; however, his name was inadvertently not added to the FDA protocol.

Change: The addition of a potential repeat baseline visit if deemed necessary by the study team.

Rationale: If a patient has a significant health status after their baseline visit, but before the scheduled surgery, the study team wants to evaluate the patient's current medical status to determine if the health status change will affect the baseline data. In the rare occasion that the study team determines the patient's baseline data will be affected, they want to ask the patient to come back to clinic for a repeat baseline visit. If the patient declines, they may still proceed with the study as planned.

Change: Update inclusion/exclusion criteria to state that the PI will have the final decision regarding patient eligibility.

Rationale: The PI wants to ensure that he has the final decision regarding patient eligibility, as there may be other factors that should be considered prior to the patient being enrolled into the study.

Change: Update the Independent Research Monitor duties.

Rationale: After discussion with the new medical monitor, the duties were updated to include specific items he would like to review.

Amendment 4

The overall reason for the amendment: To update the Independent Research Monitor to Dr. Catalin Ezaru.

Protocol Changes:

Change: Replace Dr. Chelly as the Independent Research Monitor with Dr. Catalin Ezaru.

Rationale: The Independent research monitor is being updated due to VA Credentialing issues.

Amendment 3

The overall reason for the amendment: To incorporate required Department of Defense reporting language and to update the study calendar to remove discharge day, replace the TUG test with the repeated chair stand test and add the repeated chair stand test to Post-Op days 2+.

Protocol Changes:

Change: Removed discharge day from the study calendar.

Rationale: As discharge can't be accurately predicted, it has been removed from the study calendar.

Change: Replaced TUG Test with the Repeated Chair Stand Test

Rationale: Due to logistical issues with completing the TUG test, a similar replacement test, the repeated chair stand test will be done in place of the TUG test.

Change: Added repeated chair stand test to Post-Op days 2+.

Rationale: As discharge can't be accurately predicted, the repeated chair stand test has been added to all PT sessions starting Post-Op Day two until the patient is discharged.

Change: Added DoD reporting language to section 9.0.

Rationale: The DoD has requested that this additional language be added.

Change: Minor administrative changes throughout the protocol document.

Rationale: Minor administrative and formatting changes to make the document easier to read.

Change: Addition of research staff.

Rationale: Updating the research staff list to reflect the current study team.

Amendment 2

The overall reason for the amendment: To incorporate physical therapy and orthopedic staff feedback into the protocol and to update the eligibility criteria.

Protocol Changes:

Change: Changed Post-Op follow up visits from 1 week and 1 month to 2 weeks post-op and 6-weeks post-op. Also, the 2 weeks post-op visit is now an in-person visit and is no longer a phone call.

Rationale: Updated to coordinate with patient's standard of care orthopedic post-op visits.

Change: Update the Randomization and Blinding schema.

Rationale: Updated the randomization and blinding schema as per the VAPHS Investigational Drug Service Pharmacist.

Change**:** Revised the study calendar and study visits. Updated when various questionnaires and physical therapy tests are administered.

Rationale: After discussion with the Physical Therapy team, the study calendar was updated to reflect their suggestions, along with PI requested changes.

Change**:** Added information on all questionnaires and clinical assessments, regardless of whether or not they are considered standard of care or research.

Rationale: Added information for all questionnaires and clinical assessments completed for protocol consistency. Previously not all items were listed.

Change: Updated inclusion/exclusion criteria.

Rationale: Updated the inclusion/exclusion criteria as per FDA requested changes.

Change: Updated recruitment procedures.

Rationale: After discussions with all of the involved departments (PI, Study coordinator, orthopedic department & IMPACT clinic), the recruitment strategy was updated to reflect requested changes to maximize patient recruitment.

Change: Updated external DSMB information.

Rationale: Added information regarding the external DSMB, including meeting frequency.

Change: Updated potential benefits section.

Rationale: Update the potential benefits section of the protocol to match the IRB approved language in the local VAPHS IRB application.

Amendment 1

The overall reason for the amendment: To make James Ibinson, MD a Co-Principal Investigator of the study for fiscal purposes only.

Protocol Changes:

No protocol changes.