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Ibuprofen to Decrease Opioid Use and Post-operative Pain Following Unilateral Inguinal Herniorrhaphy

Doc Date: 7/27/20

PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
(Wilford Hall Ambulatory Surgical Center – WHASC)

PROTOCOL SUMMARY

1. Title:

Ibuprofen to Decrease Opioid Use and Post-operative Pain Following Unilateral Inguinal Herniorrhaphy: A Prospective, Placebo-Controlled, Double-Blind, Randomized Controlled Trial
FWH20160095H

2.0. Principal Investigator (PI): **MOFMC PI:** **MOFMC Co-PI:**

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Rank/Corps or Civilian Rating	Maj	
Date of IRB Approved CITI Training & Date of Good Clinical Practice Training	10/26/13	
Branch of Service	USAF	
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3.0. Research Plan:

3.1. Purpose: The purpose of this study is to investigate the decrease in post-operative pain and post-operative opioid usage (oxycodone/acetaminophen), in morphine equivalent units (MEUs), following open unilateral inguinal hernia repair, between subjects taking supplemental ibuprofen to subjects not taking ibuprofen. Oxycodone/acetaminophen are commonly prescribed medications for pain control following surgical procedures. The study will investigate both opioid naïve and non-opioid naïve patients, to assess for differences in opioid medication requirements, pain relief and activity levels between these groups.

3.2. Hypotheses, Research Questions, or Objectives: To quantify the average MEUs necessary to provide adequate pain relief following an open unilateral inguinal hernia repair in adults, in order to reduce the amount of surplus opioids prescribed. To determine if the combination of ibuprofen with oxycodone (an opioid) and acetaminophen can decrease the total MEUs consumed in the post-operative period. The secondary objectives include assessing the validity of the previous findings that depressive symptoms and self-perceived risk for opioid addiction predict prolonged use of opioid medications following surgery. The secondary objective will be assessed using a depression screening questionnaire, and an opioid addiction risk questionnaire and single question. The physical activity of the subjects will also be assessed via serial questionnaires to determine if the patients taking ibuprofen have a quicker return to baseline physical activity versus the placebo-controlled groups (no ibuprofen).

4. Brief Summary of the study: This is a prospective, randomized, double-blinded, and placebo-controlled trial comparing oxycodone/acetaminophen prescribed with or without ibuprofen for pain control following open unilateral inguinal hernia repair, with allowed exception of any currently prescribed opioid (codeine, hydrocodone, hydromorphone, morphine, methadone, oxymorphone, transdermal fentanyl), which can be continued. The patients will not be allowed to continue any over-the-counter pain medications, such as ibuprofen, naproxen, or acetaminophen containing medications, that were not prescribed by the investigators during this study. Patients not receiving Ibuprofen will be given a placebo pill composed of corn starch. The placebo pill will be formulated into the same shape, size and color as the ibuprofen capsule. Neither the investigators nor the research subjects will know if the subject is receiving a placebo versus Ibuprofen. The subjects will complete pain level and medication diaries, and will be followed for 2 months after their surgery. The research aims to discover the appropriate amount of opioid medication to prescribe to patients undergoing an elective open inguinal hernia repair, and reduce the total opioid dose needed by utilizing ibuprofen in combination. We expect that the subjects who take ibuprofen will use less oxycodone/acetaminophen, and have comparable or lower mean pain levels. This could contribute to reducing the surplus opioids prescribed by physicians after surgery, which can lead to opioid use disorders. This particular procedure is common in men, and the findings have the potential to decrease the symptoms and pain of Active Duty members and DoD beneficiaries who undergo an inguinal hernia repair, and are at risk for prescription drug abuse or dependence.

5. Subjects: Active Duty members and DoD beneficiaries age 18 or older will be recruited at the MOFMC. No special populations (e.g., pregnant women, children, military basic trainees, prisoners, detainees) will be recruited.

6. Inclusion/exclusion criteria:

Inclusion:

- Active Duty members and DoD beneficiary patient 18 years or older

- Elective, open unilateral inguinal herniorrhaphy using Lichtenstein (tension free with mesh) hernia repair technique

Agree to take only the prescribed oral analgesic medication (oxycodone/acetaminophen), plus or minus ibuprofen, for the initial fourteen-day post-operative period, with allowed exception of any currently prescribed opioid (codeine, hydrocodone, hydromorphone, morphine, methadone, oxymorphone, transdermal fentanyl), which can be continued.Agree to honestly complete a depression screening questionnaire, illicit drug use personal history and questionnaire, and physical activity assessment questionnaire, with the knowledge that if the patient is an active duty member, this information could result in a referral to medical or command authorities for potential Uniform Code of Military Justice (UCMJ) violations or concerns for subject health and fitness for duty.

Exclusion:

- Subjects who are pregnant or nursing.
- Patients who refuse to complete the illicit drug use, physical activity, and depression questionnaires.
- Strangulated, incarcerated, or otherwise emergent, urgent, and non-elective inguinal herniorrhaphy.
- Those patients who are allergic to, refuse to take, or are otherwise unable to take oxycodone, ibuprofen, or acetaminophen medication orally for post-operative pain management.
- Patients on pain contracts, or under the care of a pain medicine specialist for management of chronic pain at the time of surgery.
- Subjects with serum creatinine level > 1.3 mg/dL as measured at the baseline study visit.
- Subjects with serum aspartate transaminase (AST) greater than 3 times the upper limit of normal (level >102 U/L)
- Subjects with serum alanine transaminase (ALT) greater than 3 times the upper limit of normal (level > 165 U/L)
- Subjects who do not speak, read, and write fluently in English.
- Subjects with a history of cirrhosis.
- Subjects enrolled in another clinical trial during the same period as their involvement as this study.
- Subjects, who in the investigator's opinion, will be unable to complete a pain diary or follow-up visits, or otherwise not comply with the study protocol.

7. Number of Subjects: TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): 185

8. Use of an Investigational New Drug: N/A

9. Use of an Investigational Device: N/A

10. Use of a Placebo: Yes. The placebo is a capsule filled with corn starch. The placebo will be formulated by Solutions Specialty Pharmacy in Las Vegas, Nevada, which will be responsible for the compounding of ibuprofen capsules and the manufacture of the placebo capsules. The placebo capsules will be filled with corn starch. The placebo and ibuprofen capsules will appear identical, so the subjects, research staff, and investigators remain blinded to the study assignments. The Solutions Specialty Pharmacy will label bottles of the ibuprofen and the placebo prior to delivery to the MOFMC Pharmacy. The MOFMC Pharmacy will be responsible for randomizing the patients using a random number generator, in order to maintain blinding of the patients and the investigators. The MOFMC Pharmacy will be able to un-blind the randomization if needed for an emergency medical care. The MOFMC Pharmacy will be responsible for dispensing the ibuprofen capsules, placebo capsules, and oxycodone/acetaminophen tablets. The investigators and patients will be blinded to the randomization groups.

PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
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FWH#:

2.0. Principal Investigator (PI): **MOFMC PI:** **MOFMC Co-PI:**

Name	William H. Scott, Jr., DO	
Rank/Corps or Civilian Rating	Maj	
Date of IRB Approved CITI Training & Date of Good Clinical Practice Training	10/26/13	
Branch of Service	USAF	
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Department & Base	General Surgery, Nellis Air Force Base	
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2.2. Research Assistants (RA) & Coordinators (RC):

Name	AD/DoD Civ/Ctr/ Non-DoD Civ	Rank/Corps or Civilian Rating/Title	Date of CITI Training	Phone & Pager #
Jill Clark, MBA/HCM	Ctr	Senior Research Associate/Clinical Research Manager	03/20/14	(702) 653-3298
Jennie Moss, RN, M.S.	CTR	Senior Research Associate	09/01/15	(702) 653-2113
Tracy Bogdanovich, CCRC	Ctr	Clinical Research Coordinator	04/03/14	(702) 653-2088
Lisa Stammers, RN, BSN	DoD Civ	DME Nurse	06/17/14	(702) 653-3239
Daniel Shaffer, BSBA	Ctr	Clinical Research Coordinator	06/29/15	(702) 653-2067
Heather Rider, B.S.	Ctr	Clinical Research Coordinator	07/21/15	(702) 653-2521

2.3. The research relevance of this protocol focuses on:
[] Diagnosis [X] Treatment [] Medical Utilization/Managed Care [] Prevention [] Medical Readiness [] Other

2.4. Location(s):

a. Collaborating Facilities: N/A
b. Air Force Sites seeking Regional IRB: MOFMC, Jill Clark, (702) 653-3298
c. List study sponsors: N/A

3. Research Plan:

3.1. Purpose: The purpose of this study is to investigate the decrease in post-operative pain and post-operative opioid usage (oxycodone/acetaminophen), in morphine equivalent units (MEUs), following open unilateral inguinal hernia repair, between subjects taking supplemental ibuprofen to subjects not taking ibuprofen. Oxycodone/acetaminophen are commonly prescribed medications for pain control following surgical procedures. The study will investigate both opioid naïve and non-opioid naïve patients, to assess for differences in opioid medication requirements, pain relief and activity levels between these groups

3.2. Hypotheses, Research Questions, or Objectives: To quantify the average MEUs necessary to provide adequate pain relief following an elective, open unilateral inguinal hernia repair in adults, in order to reduce the amount of surplus opioids prescribed. To determine if the combination of ibuprofen with oxycodone (an opioid) and acetaminophen can decrease the total MEUs consumed in the post-operative period. The secondary objectives include assessing the validity of the previous findings that depressive symptoms and self-perceived risk for opioid addiction predict prolonged use of opioid medications following surgery. The secondary

objective will be assessed using a depression screening questionnaire, and an opioid addiction risk questionnaire and single question. The physical activity of the subjects will also be assessed via serial questionnaires to determine if the patients with ibuprofen have a quicker return to baseline physical activity.

3.3. Significance: Prescription opioid use and opioid use disorders among Americans have steadily increased since 1999.(1)(2) The prevalence of prescription opioid use disorders reached 0.9% in 2013, and the mortality rate was 7.8 per 100,000 in 2013 among adults age 18 to64.(2) Over 90,000 emergency department visits for prescription drug overdoses occurred in 2010, with the resultant total hospital costs reaching $1.2 billion.(3) The multifaceted approach to reducing the harms from prescription opioid use disorders includes prescription drug monitoring programs, widely available naloxone, and primary prevention through education.(1) However, changing prescribing habits is an important piece of the puzzle that must not be overlooked.(1) Few studies have been done looking at opioid usage within certain post-operative groups.(4)(5)(6) In their big data retrospective review, Wunsch et al. found that the average prescription for MEU medication filled in the 7 days after an inguinal hernia repair had increased to 229 milligrams in 2012 from 212 milligrams in 2004 ($p<0.001$).(7) We also know that combining an intra-operative regional field block with post-operative acetaminophen, a non-steroidal anti-inflammatory drug, and an opioid is the recommended treatment for post-operative pain following inguinal hernia repair in adults.(8) This research aims to help guide physicians as to the appropriate dose of opioid medications that should provide a patient with adequate pain relief following a unilateral open inguinal hernia repair. We hope to decrease unnecessary opioid prescriptions, and therefore decrease overdoses and opioid use disorders, through the knowledge gained in this research.

3.4. Military Relevance: This research will provide a reference for military surgeons to adequately control post-operative pain following an inguinal hernia repair, while reducing the prescription of surplus opioids that may contribute to opioid use disorders. Opioid overdoses and use disorders are significant burdens on the mental, physical, and financial health of military members. The inguinal hernia repair is one of the most common general surgical procedures performed, with a higher incidence in men. The findings from this research have the ability to change prescribing habits for a common surgical procedure performed for military members. The findings may also translate well to other surgical procedures.

3.5. Background and Review of Literature: Prescription opioid use and opioid use disorders among Americans have steadily increased since 1999, causing more overdoses, and increasing health care costs.(1)(2)(3) A multifaceted approach to reducing the harms from prescription opioid use disorders includes prescription drug monitoring programs, widely available naloxone, and primary prevention through education.(1) However, changing prescribed habits is an important piece of the puzzle that must not be overlooked.(1) Few studies have been done looking at opioid usage within certain post-operative groups.(4)(5)(6)(9) However, Litkowski et al. looked at oxycodone and ibuprofen for post-operative pain control after oral surgery, and noted that patients had significantly less total pain and larger sum of pain intensity differences at 3 hours compared to oxycodone with acetaminophen and hydrocodone with acetaminophen.(10) Van Dyke et al showed that oxycodone with ibuprofen was more effective at controlling post-surgical dental pain than oxycodone alone.(11) While Johnson et al. found that the combination of oxycodone with acetaminophen had better analgesic effect than 400 milligrams of ibuprofen alone(12), Singla et al. found that 400 milligrams of ibuprofen resulted in superior pain relief for women after abdominal surgery when compared to 5 milligrams of oxycodone.(10) Hydrocodone with ibuprofen has also been found to have better post-operative pain reduction than oxycodone with acetaminophen.(13) Stambaugh and Drew found that the addition of 600 milligrams of ibuprofen to the pain control regimen of patients with metastatic cancer to the bone resulted in decreased use of oxycodone with acetaminophen compared to placebo.(14)

The current standard of care for post-operative pain control, following inguinal hernia repair surgery, by the investigators is 5 milligrams of oxycodone with 325 milligrams of acetaminophen, taken by mouth every 4 hours as needed for pain relief. The current standard of care for ibuprofen prescription for post-operative pain utilized by the investigators is 800 milligrams by mouth every 8 hours. Ibuprofen was chosen because it has non-steroidal anti-inflammatory properties, but has the lowest side effect profile of this class of medications. (15) (16)

The measurement of pain following surgery is another topic of the research study, with many options available to researchers. These options include visual analog scales (VAS), like the Surgical Pain Scales, numerical rating scales (NRS), verbal rating scales (VRS), or verbal numerical rating scales (VNRS).(17)(18) The NRS and VNRS have consistently been shown to be more preferred by patients, with better compliance, and with good recall correlation of the pain experienced of at least one week. (17) (19)

Many factors can potentially predict prolonged opioid use after an elective surgery, and some have been researched in studies of inguinal hernia surgery patients. Physicians are aware that certain patients are predisposed to using more opioid medication following surgery, with risk factors such as previous or current nicotine use or substance abuse.(20) Medical co-morbidities may also predispose persons to differing outcomes and medication use after surgery, and the Centers for Medicare and Medicaid Services' Hierarchical Condition Category Risk Adjustment Model is the superior tool in predicting post-operative outcomes.(21) A quick depression symptom screen known as PHQ-9 may help identify the patient population at higher risk for prolonged opioid use or opioid dependence after surgery.(22) There have been many scales and scores developed to assess functional activity following surgery, such as the Activities Assessment Scale (AAS). (23) (24) (25) The AAS has been validated in men who underwent inguinal

hernia repair, as well as women who underwent pelvic reconstructive surgery.(25)(26) These scales describe the level of activity that the patient has after surgery, and will help the researchers determine the level of physical impairment each patient is experiencing before and after surgery. A short Opioid Risk tool has also been found to identify patients at risk for displaying "aberrant behaviors" when they are prescribed opioids.(27)(28) This tool can help identify patients at risk for prolonged opioid use after surgery, and this will help the researchers determine if this tool is useful in this study population as well. We also know that patients taking opioid medication prior to an elective surgery score higher on the Beck Depression Inventory, Pittsburgh Sleep Quality Index, Screener and Opioid Assessment for Patients with Pain-Revised score, lower anxiety sensitivity, self-perceived risk of addiction, and have higher baseline pain at the surgical site and at other body sites.(29)(30)(31)(32) In their big data retrospective review, Wunsch et al. found that the average prescription for morphine equivalent medication filled in the 7 days after an inguinal hernia repair had increased to 229 milligrams in 2012.(7) We also know that combining an intra-operative regional field block with post-operative acetaminophen, a non-steroidal anti-inflammatory drug, and an opioid is the recommended treatment for post-operative pain following inguinal hernia repair in adults.(8) In fact, if patients are not given a prescription for an opioid following their ambulatory surgery, they are significantly less likely to become chronic opioid users.(33) Yet, there is no current recommendation to answer the question, "how much should I prescribe my patient after surgery?" Physicians are in danger of prescribing too few opioids, and causing their patients unnecessary pain, or prescribing too many opioids and contributing to the opioid use disorder epidemic. Given the more than $1.2 billion spent on hospital costs for inpatient prescription drug overdoses in 2010, clearly a systemic change is needed. (3) This research aims to provide physicians with a framework for the prescribing habits.

3.5.1. Bibliography:

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3.6. Research Design and Methods: Active Duty members and DoD beneficiaries age 18 or older who meet the inclusion criteria will be offered an opportunity to participate in the study at the MOFMC. The PI or AI will not recruit their own patients to prevent any misconception of coercion or undue influence. The placebo will be formulated by Solutions Specialty Pharmacy in Las Vegas, Nevada, which will be responsible for the compounding of ibuprofen capsules and the manufacture of the placebo capsules. The placebo capsules will be filled with corn starch. The placebo and ibuprofen capsules will appear identical, so the subjects, research staff, and investigators remain blinded to the study assignments. The Solutions Specialty Pharmacy will label bottles of the ibuprofen and the placebo prior to delivery to the MOFMC Pharmacy. The MOFMC Pharmacy will be responsible for randomizing the patients, in order to maintain blinding of the patients and the investigators. The MOFMC Pharmacy will be able to un-blind the randomization if needed for an emergency medical care. The MOFMC will be responsible for dispensing the ibuprofen capsules, placebo capsules, and oxycodone/acetaminophen tablets. The investigators, research staff, and patients will be blinded to the randomization groups.

Opioid medication use is common in the United States for both chronic and acute pain. Much research has been performed previously to investigate reasons for the prolonged use of opioid medications for acute pain following surgery.(29-33) This research has shown that self-perceived opioid risk, as well as depression symptoms, are independently predictive of prolonged opioid use following surgery. In order to correctly assess the effect of ibuprofen on the reduction of MEUs consumed following surgery, the confounding factors of opioid use, addiction risk, and depression need to be assessed and accounted for in each subject. This improves the internal validity of the study. If the known confounders are not accounted for a priori, then the study's results and

conclusions are substantially weakened. In addition, this study will confirm the validity of previous findings regarding prolonged post-operative opioid use based on depression symptoms and opioid addiction risk.

The depression screen previously validated for predicting prolonged opioid use following surgery is the Beck Depression Inventory-II (BDI-II). (29)(30) The PHQ-9 is another depression screen that can also be used to identify depressive symptoms.(22) Our research protocol allows for either depression screen to be utilized, but the plan will be to use the BDI-II if grant funding is obtained to purchase the rights to the tool. If funding cannot be obtained, then the open access PHQ-9 tool will be used.

Given the special population of Active Duty members, the identification of any history of substance abuse can have severe consequences for the Active Duty personnel. Likewise, the identification of any mental health issues can have severe consequences for an Active Duty member's career. These consequences must not be taken lightly by the research staff or investigators, and must be made clear to the prospective subjects at the time of screening and enrollment. The Active Duty personnel approached to consent to this study will be given a thorough explanation of the study procedures, including the collection of mental health and substance abuse questionnaires. The risk to the subject will be minimized by allowing subjects to refuse to participate in the study. Additionally, the subject's will be informed that they don't have to complete or answer any question that they do not want to. At the top of each questionnaire, a sticker will be placed that clearly states that the subject is not required to answer any or all questions, without repercussion. The informed consent process will include an explanation of potential consequences if the subject is identified as having a substance abuse history or current use of illicit drugs, or mental health illness. These consequences include reporting the illicit drug use to the commanding officer, and reporting the mental health issues to the subject's physician, and potentially to the mental health office.

Opioid withdrawal can be a deadly condition, and requires attentive care by physicians to prevent. Persons who present in acute pain following surgery are continued on their usual opioid medication, and started on a short-term higher dose medication as well.(37)(38) For this study, we will enroll patients who are both opioid naïve and opioid dependent. We will follow the standard practice of continuing the subject's usual dose of opioid medication, and add oxycodone/acetaminophen plus or minus ibuprofen or placebo. By measuring the MEUs, we will convert all opioid medications into one measurement system that allows comparison of any opioid medication to any other opioid medication, using morphine as the currency of exchange.

Screening Visit:

- Discuss the purpose of the study and the required completion of study-related questionnaires and their potential impact for active duty members. (research-driven)
- Obtain signed Informed Consent Document and HIPAA Authorization (research-driven).
- Review the patient's past medical history in Armed Forces Health Longitudinal Technology Application (AHLTA) or ESSENTRIS to verify the inclusion/exclusion criteria. (research-driven)
- We will record information from the pre-operative visits, including name, date of birth, age, phone number, current email address, gender, race, ethnicity, social security number, surgical history, family history (first degree relative) of opioid use disorder, medical history, height (in inches), weight (in pounds), waist circumference (in inches) measurement, blood pressure, temperature, pulse, respiratory rate, allergies, and medications including whether subject is taking any statins, fibrate, niacin or bile acid binding agent, opioid usage over the last 6 months. The medication record will include all current prescription and over the counter medications, including the use, frequency, and dosage. (standard of care) Specifically, the use of acetaminophen alone or in combination with other medications will be recorded. A co-morbidity score will be calculated using the Centers for Medicare and Medicaid Services' Hierarchical Condition Category Risk Adjustment Model. (research-driven)
- We will record the subject's tobacco use history, alcohol use history, marijuana use history, other illicit drug use history, and previous non-prescription use of opioids. (standard of care)
- Obtain an overall pain score, from 0 to 100, with 100 being the worst pain imaginable. (research-driven)
- Obtain a localized pain score from 0 to 100, with 100 being the worst pain imaginable, which the patient attributes specifically to the hernia that is scheduled for surgical intervention. (research-driven)
- Instruct patients to discontinue use of any over-the-counter pain medications, such as ibuprofen, naproxen, or acetaminophen containing medications, that were not prescribed by the investigators during this study.
- Subjects will have the following blood test drawn, which include (research-driven):
    - Fasting comprehensive metabolic panel (liver function, renal function, plasma glucose tests) via 1 venipuncture (5-10 milliliters, approximately 1-2 teaspoons of blood will be drawn)
      **Subject's CMP results must be within 30 days of the day of surgery or it will need to be repeated.*
    - Women of childbearing potential will have a serum pregnancy test (5-10 milliliters, approximately 1-2 teaspoons of blood) or urine pregnancy test (10 drops or less than 1 milliliter of urine) (research-driven). If needed, the additional 5-10 milliliters for the serum pregnancy test would be gathered via the same venipuncture as the fasting comprehensive metabolic panel. (standard of care)

Visit 1 (may occur the same day as the screening visit or the same day as visit 2)**:**

- The standard of care local anesthesia used for this type of surgery is bupivacaine. The surgeon will be reminded via a note in the medical record. (standard of care)
- Subjects will be randomized by the MOFMC Pharmacy into one of two naturally stratified groups (e.g., opioid naïve patients and non-opioid naïve patients), with further randomization into an opioid + ibuprofen study group or an opioid + placebo study group The research coordinator will notify the MOFMC Pharmacy if the subject is an opioid naïve patient, or a non-opioid naïve patient to assist with stratification. A random-number generator blocking will be used to ensure roughly equal sample sizes. The groups will also be stratified by the Beck Depression Inventory-II score completed on visit 1 (greater than 13, or 13 or less), and by the self-perceived risk of addiction question asked on visit 1 (score of 1 or 2, vs. 3 or 4). If the Beck Depression Inventory-II is unavailable, then the PHQ-9 score will be used, with a cutoff of 10 or greater vs 9 or less. Subjects, research staff, and research investigators will be blinded to the study group assignments (research-driven). The MOFMC Pharmacy staff will maintain a key that can be used to un-blind the randomization scheme if needed for an emergent patient care issue. Study ID numbers will be used to maintain blinding and confidentiality. (research-driven)
    - Opioid naïve patients (used an opioid for less than 14 days in the past 6 months, and no history of opioid use disorder at any time) will be randomized into one of two groups:
        - Group A: Subjects will be prescribed ibuprofen 800 milligrams by mouth every 8 hours as needed for pain for 5 days, and 1 to 2 tablets of oxycodone/acetaminophen 5 milligrams/325 milligrams (Qty. 30) by mouth every 4 hours as needed for pain for 5 days. Refills will be prescribed if needed through the period of 14 days. Subjects will be instructed to take ibuprofen preferentially if able, and only use the opioid medication as a "breakthrough medication". The total 24 hour dose of acetaminophen from all prescription and over the counter medications must not exceed 4 grams. There is a potential for liver injury if more than 4 grams of acetaminophen is consumed in one day.
        - Group B: Subjects will be prescribed 800 milligrams of a placebo pill (containing corn starch) to be taken by mouth every 8 hours as needed for pain and 1 to 2 tablets of oxycodone/acetaminophen 5 milligrams/325 milligrams (Qty. 30) by mouth every 4 hours as needed for pain for 5 days. Refills will be prescribed if needed through the period of 14 days. Subjects will be instructed to take the placebo pill preferentially if able, and only use the opioid medication as a "breakthrough medication." The total 24 hour dose of acetaminophen from all prescription and over the counter medications must not exceed 4 grams. There is a potential for liver injury if more than 4 grams of acetaminophen is consumed in one day. The placebo pill will appear identical to the ibuprofen capsules to maintain blinding. The MOFMC pharmacy can let the patient, the investigator, or treating medical personnel know your randomization group if needed in an emergency.
    - Non-Opioid naïve patients (opioid use for more than 14 days in the past 6 months, or history of opioid use disorder) will be randomized into one of two groups:
        - Group C: Subjects will be prescribed ibuprofen 800 milligrams by mouth every 8 hours as needed for pain for 5 days, in addition to their preferred opioid medication prescription. The subject's previously prescribed ("home") oral opioid medication must be one of the following medications: codeine, hydrocodone, hydromorphone, morphine, methadone, oxymorphone, or transdermal fentanyl. The doses of these home opioid medications will not be changed, but will be recorded throughout the study to allow for a statistical comparison to be made between groups. All opioid medications will be converted to MEUs to allow for comparison. If the subject is not currently taking an opioid medication, or requires more opioid medication in addition to their current opioid medication, then they will be prescribed oxycodone/acetaminophen 5 milligrams/325 milligrams (Qty. 30) by mouth every 4 hours as needed for pain for 5 days. Subjects will be instructed to take ibuprofen preferentially if able, and only use the opioid medication as a "breakthrough medication". Refills will be prescribed if needed through the period of 14 days. The total 24 hour dose of acetaminophen from all prescription and over the counter medications must not exceed 4 grams. There is a potential for liver injury if more than 4 grams of acetaminophen is consumed in one day.
        - Group D: Subjects will be prescribed or advised to continue to take only their preferred current oral opioid prescription (codeine, hydrocodone, hydromorphone, morphine, methadone, oxymorphone, or transdermal fentanyl). If they are not currently taking an opioid medication, or require more opioid medication in addition to their current opioid medication, then they will be prescribed oxycodone/acetaminophen 5 milligrams/325 milligrams (Qty. 30) by mouth every 4 hours as needed for pain for 5 days. They will also be prescribed a placebo pill (containing corn starch) to be taken by mouth every 8 hours as needed for pain. Subjects will be instructed to take the placebo pill preferentially if able, and only use the opioid medication as a "breakthrough medication." Refills will be prescribed if needed through the period of 14 days. The total 24 hour dose of acetaminophen from all prescription and over the counter medications must not exceed 4 grams. There is a potential for liver injury if more than 4 grams of acetaminophen is consumed in one day. The placebo pill will appear identical to the ibuprofen capsules to maintain blinding. The MOFMC pharmacy can let the patient, the investigator, or treating medical personnel know your randomization group if needed in an emergency.

- Subjects will complete the Beck Depression Inventory-II or the Patient Health Questionnaire (PHQ-9) depression screen, and it will be reviewed on the same day of completion. (research-driven)
- Subjects will complete the Pre-Operative Activities Assessment Scale (AAS), and it will be reviewed on the same day of completion. (research-driven)
- Subjects will complete the Opioid Risk Tool (ORT) , and it will be reviewed on the same day of completion. (research-driven)
- Subjects will be asked "How likely do you think it is that you will develop an addiction problem from pain medication you take after surgery?" and chose from 1 of 4 answers: 1: "not at all"; 2: "unlikely"; 3: "somewhat likely"; or 4: "very likely". (research-driven)
- Subjects will be asked "On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what is your average level of pain at rest in the past 24 hours?" (research-driven)
- Subjects will be asked "On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your lowest level of pain when at rest in the past 24 hours? (research-driven)
- Subjects will be asked "On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your highest level of pain when at rest in the past 24 hours? (research-driven)
- Subjects will be given a Medication and Pain Level Diary and will be instructed to complete it every day for 14 days beginning after their surgery. The subjects will be instructed to begin recording their average pain number, highest pain number, and lowest pain number beginning 24 hours post-surgical incision. The research coordinator will annotate this on the diary. They will also be instructed to record the total milligrams of each medication used in the previous 24 hours. We will issue them a new one at the 14-day visit to help them keep track but we will not collect it at the end of the study. (research-driven)
- We will record information from the subjects' surgery, for example: the start and end times of surgery and anesthesia, how long the surgery lasted, how difficult the surgery was, were the ilioinguinal, genitofemoral, or iliohypogastric nerves identified and were they protected, injured, or transected, and which opioids the anesthesiologist gives at any point during the case after incision. (research-driven)
- The preoperative instructions will include standardized verbal and written instructions: "After your surgery, it is expected that you will experience a certain amount of pain for a short period of time. You will be prescribed pain medication that you should take only when you are in pain. If you are no longer experiencing pain, you should stop taking the medication. If you do not require all of the pain medication that was prescribed, you should record the amount of medication that was unused and then properly dispose of the remainder." (standard of care)

Visit 2 (day of surgery-prior to surgery):

- Subjects will receive prescriptions for medications according to their randomization group. These prescriptions will be filled at the MOFMC pharmacy, which will perform the subjects' randomization assignments. The ibuprofen and placebo capsules will be delivered to the MOFMC Pharmacy after being compounded by Solutions Specialty Pharmacy. (research-driven)
- Subjects will complete the Pre-Operative AAS (approximately 5 minutes to complete), and it will be reviewed on the same day of completion. (research-driven)
- Research staff will record the start and end times of the surgery, record the amounts of standard of care pain medications used during their hospital stay, document any standard of care pain assessments that were performed, and document the anesthesia the subject received. (research-driven)
- Subjects will be reminded in the Post Anesthesia Care Unit (PACU) to complete their Medication and Pain Level Diary and reminded to complete it every day for the 60 days beginning after they are discharged from the hospital. (research-driven)

Visit 3 (Post-Op day 0 Contact (at time of discharge from post-anesthesia care unit)):

- Subjects will be contacted by research team in person or via telephone and asked the following questions in this order (research-driven):
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what is your average level of pain when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your lowest level of pain when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your highest level of pain when at rest in the past 24 hours?
  - What pain medications are you taking including the strength (in milligrams), and how many total doses have you taken since your surgery? Time of last opioid medication taken?
  - My relief from starting pain is: 0 = none, 1= a little, 2 = some, 3 = a lot, 4 = complete
- Subjects will be reminded to complete their Medication and Pain Level Diary. (research-driven)

Visits 4-8 (Post-op Day 1 through Day 5 Contact (each visit every 24 hours plus or minus 4 hours visit window):

- Subjects will be contacted by research team in person or via telephone and asked the following questions in this order (research-driven):

- On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what is your average level of pain when at rest in the past 24 hours?
- On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your lowest level of pain since your when at rest in the past 24 hours?
- On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your highest level of pain since your when at rest in the past 24 hours?
- What pain medications are you taking including the strength (in milligrams), and how many total doses have you taken since your last study visit? Time of last opioid medication taken?
- My relief from starting pain is: 0 = none, 1= a little, 2 = some, 3 = a lot, 4 = complete

- Subjects will complete the Post-Operative AAS, and it will be reviewed on the same day of completion. (research-driven)
- Subjects will be reminded to complete their Medication and Pain Level Diary. (research-driven)

Visit 9 (Post-Op day 14 Contact (plus or minus 2 day visit window)):

- Subjects will be contacted by research team in person or via telephone at their Post-Operative Follow Up Visit and asked the following questions in this order (in-person) (research-driven):
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what is your average level of pain when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your lowest level of pain since your when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your highest level of pain since your when at rest in the past 24 hours?
  - What pain medications are you taking including the strength (in milligrams), and how many total doses have you taken since your last study visit? Time of last opioid medication taken?
  - My relief from starting pain is: 0 = none, 1= a little, 2 = some, 3 = a lot, 4 = complete
- Subjects will complete the Post-Operative AAS, and it will be reviewed on the same day of completion. (research-driven).
- Subjects will return their Medication and Pain Level Diary and be issued a new one for the remainder of the study. (research-driven)
- Subjects will be reminded of the two remaining contacts. (research-driven)

Visit 10 (Post-Op day 30 Contact (plus or minus 5 day visit window)):

- Subjects will be contacted by research team in person or via telephone and asked the following questions in this order (research-driven):
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what is your average level of pain when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your lowest level of pain since your when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your highest level of pain since your when at rest in the past 24 hours?
  - What pain medications are you taking including the strength (in milligrams), and how many total doses have you taken since your last study visit? Time of last opioid medication taken?
  - My relief from starting pain is: 0 = none, 1= a little, 2 = some, 3 = a lot, 4 = complete
- Subjects will complete the Post-Operative AAS, and it will be reviewed on the same day of completion. (research-driven).
- Subjects will be reminded to complete their Medication and Pain Level Diary. (research-driven)

Visit 11 (Post-Op day 60 Contact (plus or minus 5 day visit window)):

- Subjects will be contacted by research team in person or via telephone and asked the following questions in this order (research-driven):
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what is your average level of pain when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your lowest level of pain since your when at rest in the past 24 hours?
  - On a scale of 0-100, with 0 being no pain and 100 being the worst pain imaginable, what was your highest level of pain since your when at rest in the past 24 hours?
  - What pain medications are you taking including the strength (in milligrams), and how many total doses have you taken since your last study visit? Time of last opioid medication taken?
  - My relief from starting pain is: 0 = none, 1= a little, 2 = some, 3 = a lot, 4 = complete
  - Were you diagnosed with post-operative neuralgia at any point following your surgery?
  - Were you diagnosed with an inguinal hernia recurrence at any point following your surgery?

- Were you diagnosed with a surgical site infection at any point following your surgery?
- Subjects will complete the Post-Operative AAS, and it will be reviewed on the same day of completion. (research-driven).
- The Medication and Pain Level Diary will not be collected from the patient. (research-driven)

Research has shown that a Verbal Numerical Rating Scale of 0-100 (VNRS-101) is a valid instrument for assessing post-operative pain, and provides a similar level of accuracy as the Visual Analog Scale (100 millimeter). (17) The VNRS-101 allows the researchers to gain greater precision in the patient's pain intensity, without requiring the use of an in-person visit to measure the pain level using a ruler.

Subjects entering the study with a current prescription for one of the listed opioid medications (codeine, oxycodone, hydrocodone, morphine, methadone, oxymorphone, hydromorphone, or transdermal fentanyl) will be allowed to continue taking these opioid medications during the study. Persons who take opioid medications long-term are at risk from opioid withdrawal if they cease taking these medications. The investigators won't know a priori what each dose will be for each subject, but the investigators will record all opioid medication used as a data point. The doses of all opioid medications will be gathered and converted to morphine equivalent units for comparison and statistical analysis.

Baseline laboratory values will be obtained to ensure no underlying kidney or liver disease, which could be exacerbated by the study medications. If the subject's AST or ALT are greater than 3 times the upper limit of normal (AST level > 102 U/L, ALT level > 165 U/L), then they will be screen failed. If the subject's creatinine is greater than 1.3 mg/dL, then they will be screen failed.

Though there are multiple techniques for hernia repair, the standard tension free mesh repair (Lichtenstein repair) is one of the most common techniques preformed and is accepted as a standard of care procedure. A polypropylene mesh will be used in all patients. A field block of the ipsilateral ilioinguinal nerve and surrounding subcutaneous tissue will be performed during the surgery in all patients, using 10 milliliters of 0.25% bupivacaine local anesthesia. The start and end times of surgery and anesthesia will be recorded, and the end time of anesthesia will be used for the time zero. To prevent confounders, no epidural or spinal anesthesia may be done for study subjects. All opioid medications given during the surgery will be recorded.

Medication usage will be plotted over the post-operative period and average opioid quantities consumed calculated based upon the information gathered, after conversion to MEU for each opioid used. Follow-up period for 60 days will include contacts post-op day 1, 2, 3, 4, 5, 14 +/- 2 days, 30 +/- 5 days, and post-op day 60 +/- 5 days.

3.6.1. Interventions, Observations, or Data Sought: Pain intensity levels and total opioid use in MEUs used by the study subjects to treat their post-operative pain with or without a combination of supplemental ibuprofen.

3.6.2. Data Collection and Processing: Data will be collected and recorded in a spreadsheet. At the conclusion of the study, all personally identifying information will be removed prior to analysis.

3.6.3. Setting: Active Duty members and DoD beneficiaries age 18 years or older will be recruited at the MOFMC. No special populations (e.g., pregnant women, children, military basic trainees, prisoners, detainees) will be recruited.

3.6.4. Date(s): November 2016-November 2018

3.6.5. Source of Research Material: Source of Research Material per Participant (Procedures)	**# Routine Care**	**# Research Driven**	**# Total Procedures**
Fasting Comprehensive Metabolic Panel	0	1	1
Women of childbearing potential will have a serum or urine pregnancy test	0	1	1
Beck Depression Inventory-II or PHQ-9 depression screen	0	1	1
Opioid Risk Tool (ORT)	0	1	1
Pre-Operative Activities Assessment Scale (AAS)	0	2	2
Post-Operative Activities Assessment Scale (AAS)	0	8	8
Medication and Pain Level Diary	0	2	2
Pain Scale (lowest)	0	10	10
Pain Scale (average)	0	10	10
Pain Scale (highest	0	10	10

3.6.6. Subjects: Active Duty members and DoD beneficiaries age 18 years or older who are scheduled for an elective unilateral inguinal herniorrhaphy will be recruited at the MOFMC. No special populations (e.g., pregnant women, children, military basic trainees, prisoners, detainees) will be recruited.

3.6.7. Inclusion/Exclusion Criteria:

Inclusion:

- Active Duty members and DoD beneficiary patient 18 years or older
- Elective, open unilateral inguinal herniorrhaphy using Lichtenstein (tension free with mesh) hernia repair technique
- Agree to take only the prescribed oral analgesic medication (oxycodone/acetaminophen), plus or minus ibuprofen, for the initial fourteen-day post-operative period, with allowed exception of any currently prescribed opioid (codeine, hydromorphone, morphine, methadone, hydrocodone, oxymorphone, transdermal fentanyl), which can be continued.
- Agree to honestly complete a depression screening questionnaire, illicit drug use personal history and questionnaire, and physical activity assessment questionnaire, with the knowledge that if the patient is an active duty member, this information could result in a referral to medical or command authorities for potential Uniform Code of Military Justice (UCMJ) violations or concerns for subject health and fitness for duty.

Exclusion:

- Subjects who are pregnant or nursing.
- Patients who refuse to complete the illicit drug use, physical activity, and depression questionnaires.
- Strangulated, incarcerated, or otherwise emergent, urgent, and non-elective inguinal herniorrhaphy.
- Those patients who are allergic to, refuse to take, or are otherwise unable to take oxycodone, ibuprofen, or acetaminophen medication orally for post-operative pain management.
- Patients on pain contracts, or under the care of a pain medicine specialist for management of chronic pain at the time of surgery.
- Subjects with serum creatinine level > 1.3 mg/dL as measured at the baseline study visit.
- Subjects with serum aspartate transaminase (AST) greater than 3 times the upper limit of normal (level >102 U/L)
- Subjects with serum alanine transaminase (ALT) greater than 3 times the upper limit of normal (level > 165 U/L)
- Subjects who do not speak, read, and write fluently in English.
- Subjects with a history of cirrhosis.
- Subjects enrolled in another clinical trial during the same period as their involvement as this study.
- Subjects, who in the investigator's opinion, will be unable to complete a pain diary or follow-up visits, or otherwise not comply with the study protocol.

3.6.8. Instrumentation: N/A

4.0. Human Subject Protection:

4.1. Recruitment: All potentially eligible patients, presenting to the Surgery Department for a unilateral inguinal herniorrhaphy, will be offered an opportunity to participate. Some patients may be patients of the PI or AI, however, they will have the research team recruit their patients to prevent any misconception of coercion or undue influence. When a potential subject is identified by the treating physician, the Research Staff will be contacted to speak with the patient directly. Surgery Department staff will ask the patient if they are willing to speak with the research staff and, if they agree, then the research staff will be contacted to come discuss the study with the potential participant. An advertisement will be placed in the Surgery Department.

4.2. Consent Processes: Informed Consent and HIPAA authorization will be sought in advance of any study-related procedures from each prospective subject and appropriately documented in accordance with 32 CFR 219.117. Potential candidates will be notified about the study either through posted advertisements or by their care provider and will be given the opportunity to consent by one of the referred study coordinators. The study coordinator will provide a written copy of the Informed Consent Document (ICD). The subject may decline to consent without prejudice. At the subjects' discretion, they may take the ICD home to discuss further prior to making a decision and if they decide they are interested in participating, they can contact the research department the next time they present to the Surgery Department. If the subject consents, a copy of the ICD will be given to the subject. No vulnerable populations are included in this research study. Subjects who cannot provide Informed Consent will not be allowed to participate. No Legally Authorized Representatives (LAR) will be utilized.

4.3 Participation Compensation: Subjects will not be paid for participation in this study.

4.4. Assent Process: N/A

4.5. Benefits: There may be no direct benefits to the subjects for participating in this study. The indirect benefit of this study includes the benefit to the military members and society at large regarding the increased knowledge of post-operative pain management learned from the results of this study.

4.6. Risks: There is a risk of inadvertent breach of confidentiality. The potential risks to participate in this study are minimal and include:

The risks and side effects of the standard of care opioid medication given during this study will be provided by the pharmacy along with the standard of care prescriptions. Opioid medications such as oxycodone are strong painkillers, and have the potential to be abused and can be habit-forming for some persons. It is important to take only the necessary amount of opioid medication to relieve your pain to reduce the risk of developing addiction.

The risks and side effects associated with the venipuncture (Blood Draw), although not likely, include pain, bleeding, bruising, feeling light-headed, and a slight possibility of infection

The placebo is a capsule filled with corn starch. There is a chance, although not likely, that subjects have an allergic reaction. The signs and symptoms of an allergic reaction include:

LESS LIKELY and not serious	RARE and serious
Hives or skin rash; nausea, stomach cramps, indigestion, vomiting or diarrhea; stuffy or runny nose, sneezing, headaches, asthma.	Anaphylaxis (a potentially life-threatening reaction that impairs breathing and sends the body into shock)

DRUG NAME	LIKELY and not serious	LESS LIKELY and not serious	RARE and serious
Ibuprofen	difficulty with bowel, movements; drowsiness, lack of strength; relaxed and calm feeling; sleepiness or unusual drowsiness	upset stomach; heartburn; diarrhea; constipation; bloating; gas; dizziness; headache; nervousness; skin itching or rash; blurred vision; ringing in ears	nausea; stomach pain; itching, weight gain; discolored urine or stool; jaundice (yellowing of skin or eyes); severe headache; neck stiffness; chills; increased sensitivity to light; bruising; numbness; tingling; muscle weakness; fever; sore throat

Rare and serious

- There is a risk that completing the Beck Depression Inventory II, Patient Health Questionnaire (PHQ-9) depression screen, Opioid Risk Tool (ORT) and/or the Activities Assessment Scale (AAS) may identify a subject as at risk for a mental health condition or a substance abuse problem and result in a referral to medical or command authorities for potential Uniform Code of Military Justice (UCMJ) violations or concerns for subject health and fitness for duty.

4.7. Costs: N/A

4.8. Safeguards for Protecting Information: The research consents will be stored in a locked cabinet in a locked room. Medical records will be annotated with ICD-10 code Z00.6 to reflect the subject's participation in a research study. All research data including identifiable patient demographics will be kept in a separate electronic database, which will be encrypted, double password protected and the access will be restricted. The research data will be coded and any links to identifiable data will be destroyed (an approved shredding bin) as soon as the Final Report Approval has been obtained from the IRB. The anonymized research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval. The Master Key will be maintained by the MOFMC Pharmacy, and will have exclusive access to the key in the event of an adverse medication reaction.

4.9. Safeguards for Protecting Subjects: The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and oversight staff for confirmation of the study data.

4.9.1. Minimizing Risks: The participants will be monitored by their surgeon, in addition to the research team, principal investigator, and co-investigators. Subjects will have access to study personnel should they have any issues, and the study staff and investigator contact information will be given to all subjects when enrolled. If there are any adverse events or medical emergencies, they will be immediately reported to one of the Investigators and an applicable medical evaluation will be initiated. The MOFMC Pharmacy will maintain the Master Key for the randomization, and the protocol assignment will be unblended if necessitated and requested by the treating medical personnel. Adverse events that could require breaking the protocol would be any medical condition which is suspected to be related to the ibuprofen or placebo medication. This conditions could include anaphylaxis, respiratory failure, altered mental status, hives, angioedema, acute kidney injury, or other symptoms of allergic reaction. In an intention to treat analysis, the un-blinded patients will still be analyzed according to their randomization. In a per protocol analysis, the un-blinded patients will be excluded from the analysis, given their deviation from the protocol. Given the special population of Active Duty members, the identification of any history of substance abuse can have severe consequences for the Active Duty personnel. Likewise, the identification of any mental health issues can have severe consequences for an Active Duty member's career. These consequences must not be taken lightly by the research staff or investigators, and must be made clear to the prospective subjects at the time of screening and enrollment. The Active Duty personnel approached to consent to this study will be given a thorough explanation of the study procedures, including the collection of mental health and substance abuse questionnaires. The risk to the subject will be minimized by allowing subjects to refuse to participate in the study. Additionally, the subject's will be informed that

they don't have to complete or answer any question that they do not want to. At the top of each questionnaire, a sticker will be placed that clearly states that the subject is not required to answer any or all questions, without repercussion. The sticker will state: "You are not required to complete any or all questions on this questionnaire." It will be made abundantly clear that Active Duty Members are given the option of completing all, part, or none of the questionnaires. The informed consent process will include an explanation of potential consequences if the subject is identified as having a substance abuse history or current use of illicit drugs, or mental health illness. These consequences include reporting the illicit drug use to the commanding officer, and reporting the mental health issues to the subject's physician, and potentially to the mental health office.

If a positive affirmation on a drug or alcohol questionnaire is identified, then this will be reported to command/law enforcement by an Active Duty investigator. If a positive affirmation on a mental health questionnaire is identified, then that will result in a referral to mental health, and could potentially result in a medical evaluation board (MEB).

We will place the subject ID number on all questionnaires in lieu of the subject name to protect confidentiality.

4.9.2. Vulnerable Populations: N/A

4.9.3. Clinical Care: All subjects will receive standard of care regardless of inclusion into this study. If at any time a subject experiences any injury or adverse effects, appropriate clinical care will be given or subject will be referred to appropriate provider. The MOFMC Pharmacy will maintain the Master Key for the randomization, and the protocol assignment will be un-blinded if necessitated and requested by the treating medical personnel. Adverse events that could require breaking the protocol would be any medical condition which is suspected to be related to the ibuprofen or placebo medication. This conditions could include anaphylaxis, respiratory failure, altered mental status, hives, angioedema, acute kidney injury, or other symptoms of allergic reaction. In an intention to treat analysis, the un-blinded patients will still be analyzed according to their randomization. In a per protocol analysis, the un-blinded patients will be excluded from the analysis, given their deviation from the protocol. In the event a subject makes a positive affirmation on a drug or alcohol questionnaire, an Active Duty research staff member will report it to command. If a subject is identified as at risk for a mental health condition or a substance abuse problem during the study, the Active Duty Principal Investigator will report the information immediately to mental health.

4.9.4. Injury Compensation: N/A

4.9.5. Data Safety Monitoring: The principal investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and oversight staff for confirmation of the study data.

5.0. Alternatives: The alternative is to receive standard of care and not to participate in this study.

6.0. Data Analysis:

6.1. Outcome Measures: The primary outcome measure is morphine equivalent units (MEU; milligrams) at 8 repeated measurements over the first 120 hours of the study. Secondary outcome measures are MEU at 2 repeated measurements over 14 days and 60 days of the study, sum of the pain intensity difference (SPID) at 24 hours, 48 hours, 72 hours, 96 hours, and 120 hours post-surgery, total pain relief (TOTPAR) at 120 hours and 336 hours (14 days) post-surgery, and Activities Assessment Scale (AAS) at 11 repeated measurements over the 60-day course of the study. The AAS will assess physical activity of the subjects via serial questionnaires to determine if the patients with ibuprofen have a quicker return to baseline physical activity.

The use of the BDI-II or PHQ-9 depressive symptom screen and the Opioid Risk Tool and self-perceived risk for opioid addiction will assist the investigators in stratifying patients into groups to account for these known confounders. A tertiary outcome measure will be to assess the validity of these tools in predicting prolonged use of opioid medications following surgery. However, the primary reason for these tools is to account for confounding factors in the primary analysis.

6.2. Sample size estimation/power analysis: For the primary outcome measure of MEU, we wish to detect a difference greater that 1 SD among treatment groups. Prior research (7) indicates patients who have undergone inguinal hernia repair will have a mean MEU of 229 mg with 107 SD at 168 hours. Using this outcome measure, a priori power for H_0 was assessed using G*Power Version 3.1.9.2. (34) The results shown below indicate a total of 160 subjects for each of the four treatment groups and two covariates, BDI and ORT having two categories each for a total of 16 groups, with 10 repeated measures will have a power of 0.973 at $\alpha = 0.05$ to detect a 1 SD difference in MEU over repeated measures. A power of this magnitude for the rANOVA will ensure sufficient power for post hoc tests having smaller sample sizes. An interim analysis may be performed to determine if results have achieved sufficient power to terminate data collection early.

F tests - ANOVA: Repeated measures, between factors
Input:
Effect size f = 0.44 (moderate)

β/α ratio = 1 (β=0.05, α=0.05)
Total sample size = 160
Number of groups = 16
Number of measurements = 10
Corr among rep measures = 0.8
Output:
Noncentrality parameter λ = 37.8
Critical F = 1.90
Numerator df = 15.0
Denominator df = 144
α err prob = 0.027
β err prob = 0.027
Power (1-β err prob) = 0.973

6.3. Statistical Analysis: The experimental design of this study is a mixed effects, randomized complete block design with repeated measures. Subject is a random effect as the subjects are a sample randomly selected and randomly assigned to treatment and covariate groups. Time of repeated measure and treatment group are fixed effects as these effects cannot be generalized to other treatments and times. Statistical analysis will be performed with R Version 3.2.4. (35)

Sample means and standard errors of measurement will be calculated for normally distributed interval variables and medians and interquartile ranges (IQR) for non-normally distributed interval variables. Frequency distributions of nominal and ordinal variables will be calculated. Null hypotheses of repeated measures will be tested by a mixed effects repeated measures analysis of variance (rANOVA), and with appropriate parametric or non-parametric mean/median comparison tests for other variables. In the event the rANOVA null hypothesis is rejected, contrasts will be used to investigate effects and differences within time intervals. In the event multiple comparison tests are used to investigate effects, the Bonferroni method will be used to correct the level of significance for α to p=0.05. (36)

Mr. Danny Sharon, Senior Research Biostatistician Subject Matter Expert for Clinical Research Management under contract W911QY-11-D-0065, is the statistical consultant support for this study.

6.4 Number of Subjects:

Number of subjects planned for MOFMC	Enrolled in Study	185	to result in	160	completing the study.

TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): 185

7. Duration of Study: Approximate duration of the study: 24 months
8. Local and External Support Services: None.
9. Intramural (GME) and Extramural Funding Support: None.
10. Conflict of Interest: None
11. Use of an Investigational New Drug, use of a Drug for a non-FDA approved purpose, use of an investigative device or use of a placebo:

This research uses an Investigational New Drug	**[] YES**	**[X] NO**
This research uses a FDA approved drug for a non-FDA approved purpose	**[] YES**	**[X] NO**
This research uses an Investigational Device	**[] YES**	**[X] NO**
This research uses a placebo.	**[x] YES**	**[] NO**

12. Medical Research Area for the Study: (Pick as many as appropriate)

[] Analytical Chemistry	[] Anatomy	[] Anesthesiology	[] Biochemistry
[] Cardiovascular Surgery	[] Cardiology	[] Cell Biology	[] Dentistry
[] Dermatology	[] Dietetics	[] Electrophysiology	[] Endocrinology
[] Emergency medicine	[] Gastroenterology	[X] General Surgery	[] Hematology
[] Histology	[] Immunology/Allergy	[] Infectious Disease	[] Microbiology
[] Molecular Biology	[] Neonatology	[] Neurology	[] Neurosurgery
[] Nursing	[] OB/GYN	[] Occupational Medicine	[] Occupational Therapy
[] Oncology	[] Ophthalmology	[] Oral/Maxillofacial Surgery	[] Orthopedics
[] Pathology	[] Pediatrics	[] Pharmacology	[] Physical Therapy
[] Mental Health	[] Radiology/Imaging	[] Urology	[] Wellness
[] Other (state):			

13. Attachments:

1. Form A-Signature Sheet

2. Form A2-Study Personnel
3. Advertisement
4. Placebo Justification
5. Informed Consent Document
6. HIPAA Authorization Document
7. Form O: Use of a Drug in Research
8. Beck Depression Inventory-II (BDI-II)
9. Patient Health Questionnaire (PHQ-9) depression screen
10. Medication and Pain Level Diary
11. Opioid Risk Tool (ORT)
12. Activities Assessment Scale (AAS)
13. Centers for Medicare and Medicaid Services' Hierarchical Condition Category Risk Adjustment Model