Cover Page

Title: Comparison of Intramuscular Ketorolac at Two Single-Dose Regimens for Treatment of Acute Musculoskeletal Pain in a Military Emergency Department: A Randomized Controlled Non-Inferiority Trial

NCT: Not received yet

Date: 2/5/2021

Note: The following document is the final copy of my protocol submitted through the Department of Army's eIRB portal. This is a standard copy, which has not been manipulated.

EIRB Protocol Template (Version 1.9)

1.0 General Information

***Please enter the full title of your study:**

Comparison of Intramuscular Ketorolac at Two Single-Dose Regimens for Treatment of Acute Musculoskeletal Pain in a Military Emergency Department: A Randomized Controlled Non-Inferiority Trial

***Please enter the Protocol Number you would like to use to reference the protocol:**

Intramuscular Ketorolac at Two Single-Dose Regimens
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
○	**Army** - William Beaumont Army Medical Center (WBAMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Turner, Nathaniel James, MPAS

Select if applicable

☐ Student ☐ Site Chair
☑ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Bongiorno, Joseph Roger, MSPA
Associate Investigator

Katoski, Timothy Paul, CPT
Associate Investigator

B) Research Support Staff

3.3 *Please add a Protocol Contact:

Turner, Nathaniel James, MPAS

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 * Has another IRB/HRPP reviewed this study or will another IRB/HRPP be reviewing this study? If Yes, answer the questions according to the IRB/HRPP Determination.

○ Yes ◉ No

IRB Name	Review Date	Determination
No records have been added		

4.2 * Is this a research study or a Compassionate Use/Emergency Use/HUD project?

◉ Yes ○ No

4.3 What type of research is this?

- ☑ Biomedical Research
- ☐ Clinical trial (FDA regulated)
- ☐ Behavioral Research
- ☐ Educational Research
- ☐ Psychosocial Research
- ☐ Oral History
- ☐ Other

4.4 Are you conducting this project in pursuit of a personal degree?

◉ Yes ○ No

4.6 * Is this human subjects research? (As defined by 32 CFR 219)

Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

(•) Yes ( ) No

4.7 * Do you believe this human subjects research is exempt from IRB review?

( ) Yes (•) No

5.0 Personnel Details

5.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

No records have been added

5.2 Will you have a Research Monitor for this study?

(•) Yes
( ) No
( ) N/A

Research Monitor Qualifications
Ensure the individual has expertise consistent with the nature of risk(s) identified within your study and is independent of the team conducting the research.

Research Monitor Role:

MAJ Lisa Jin
lisa.m.jin.mil@mail.mil
254-226-0826
Research monitor - protocol oversight, stop research/protocol if there are safety concerns, report observations to IRB, review study monitoring plan

If applicable, you may nominate an individual to serve as the Research Monitor:

	Selected Users
☐	Lisa Marie Jin, MAJ

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

( ) Yes (•) No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
No records have been added		

Total amount of funding:

0

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

If Yes, complete and attach Conflict of Interest forms for all key personnel

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

8.2 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added						

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added					

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.4 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ○ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Ketorolac, intramuscular, analgesia, pain, emergency department

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Ketorolac tromethamine is one of the most commonly used parenteral analgesics in the emergency department (ED) for the treatment of moderate to severe pain.[2] It is a nonsteroidal anti-inflammatory drug (NSAID) that belongs to a group of non-opioid analgesics that primarily inhibit the activity of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes and block the synthesis of prostaglandins and thromboxanes.[3] It has high COX-1 enzyme selectivity, a half-life of 2.4 to 8.6 hours, and is extensively metabolized in the liver and eliminated through the kidneys.[3]

There is limited evidence demonstrating increased analgesic effect with higher doses of ketorolac. Kantorovich et al. concluded that 10 mg is the analgesic ceiling dose for both intravenously and intramuscularly administered ketorolac.[10] The analgesic ceiling is the dose of a drug beyond which further dosage increase results in no additional analgesic effect.[11] Staquet demonstrated in cancer patients with moderate to severe pain that a dose of 10 mg delivered via intramuscular injection (IM) was effective in relieving pain and associated with fewer side effects.[12] Further studies have corroborated these findings. A study conducted by Reuben and colleagues studied different doses of intravenous (IV) ketorolac as an adjunct to morphine sulfate in patients who had spinal stabilization surgery. The results suggest that increasing the doses of ketorolac did not increase the efficacy of the drug, and the 7.5 mg dose had the same efficacy as larger doses.[13] Minotti et al performed a double-blinded study that compared the analgesic effects of ketorolac 10 mg IM, ketorolac 30 mg IM, and diclofenac 75 mg IM in 180 cancer patients. The results demonstrated no difference in pain relief among all three groups.[14] Other studies have also demonstrated similar results for postoperative patients.[15,16]

The most recent study comparing different ketorolac dosing regimens on emergency department patients also support previous studies demonstrating an analgesic ceiling. The most recent of which is a study conducted by Motov et al. who evaluated the analgesic efficacy of three different doses of IV ketorolac including 10 mg, 15 mg, and 30 mg doses in 240 emergency department patients who suffered from acute pain.[1] This randomized, double-blind clinical trial determined similar efficacy in patient pain reduction scores across all three doses of ketorolac within 30 minutes.

Despite studies indicating the non-inferiority of a lower parenteral dose of ketorolac, it continues to be dosed higher than the proposed analgesic ceiling dose, particularly in the emergency department. Soleyman-Zomalan and colleagues investigated the patterns of ketorolac dosing conducted by emergency physicians, and their data indicated that ketorolac was prescribed above the 10 mg ceiling dose in 97% of patients receiving intravenous doses and 96% of patients receiving intramuscular doses.[1,7] This pattern of emergency department prescribing may be explained by the fact that 10 mg is lower than the parenteral dosing regimen recommended in emergency medicine textbooks and by the Food and Drug Administration (approved doses of 30 mg intravenously and 60 mg intramuscularly for patients younger than 65 years).[18,19] Additionally, ketorolac is stored and packaged by the manufacturer in 15 mg/mL, 30 mg/mL, and 60 mg/2mL vials, which complicates alternate dosing calculations of ketorolac.

Current standard of practice for the treatment of acute musculoskeletal pain is provider dependent. Additionally, it depends on the chief complaint, examination, and clinical picture. For non-critical acute MSK patients options are generally oral NSAIDs and IM NSAIDs. It is medical standard of care to not prescribe or administer opioids for musculoskeletal pain in the ED, unless the injury is severe (such as a long bone fracture or dislocation of a large joint). However, even in these circumstances nerve blocks and hematoma blocks may be attempted to attenuate the pain prior to administration of IV or IM opioids. Therefore, non-opioid analgesics, such as acetaminophen or Toradol are logically the first analgesics used by many providers to control the pain caused by minor musculoskeletal injuries. In general, the most common dosages for intramuscular administration of Toradol is either 30 mg or 60 mg. The most common intravenous dosing for Toradol is 15 mg or 30 mg

9.3 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

Purpose: The purpose of this study is to evaluate the effectiveness of 15 mg ketorolac versus 60 mg ketorolac injected intramuscularly for the treatment of acute musculoskeletal pain in military emergency department patients.

The alternative hypothesis is that 15 mg intramuscular ketorolac will be non-inferior when compared to 60 mg intramuscular ketorolac for the treatment of acute musculoskeletal pain in military emergency department patients.

The null hypothesis is that 15 mg intramuscular ketorolac will be inferior when compared to 60 mg intramuscular ketorolac for the treatment of acute musculoskeletal pain in military emergency department patients.

9.4 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This study utilizes a single-blinded, randomized controlled non-inferiority trial design.

9.5 Target Population:

Describe the population to whom the study findings will be generalized

The target population is DoD service members, DoD beneficiaries, and Veteran Affairs beneficiaries, 18-55 years of age, evaluated and treated at William Beaumont Army Medical Center (WBAMC) Emergency Department (ED) El Paso, Texas with a diagnosis of acute musculoskeletal pain.

9.6 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

It is the primary aim of the study to demonstrate that low dose intramuscular ketorolac, 15 mg, is not inferior to high dose intramuscular ketorolac, 60 mg, for the treatment of musculoskeletal pain. In proving the primary aim of the study, it is our hypothesis that the total man hours lost will decrease as a results of better pain management at the time of presentation to the emergency department. Second, by demonstrating that the lower dose is not inferior, this study may help increase patient satisfaction scores within military emergency departments. Lastly, by providing evidence with this single-blind, non-inferior study, it may be inferred that our results will add to the current set of literature which could become a pathway to building a larger multi-center study.

During his tenure, the previous Chief of Staff for the Army, GEN Mark Miley, clearly maintained that readiness is the priority of the U.S. Army[21]. The military medical community is front and center in maintaining the DoDs level of readiness. This study aims to demonstrate that low dose intramuscular ketorolac is not inferior to high dose intramuscular ketorolac. By demonstrating non-inferiority, it is postulated that patients receiving the lower dose of ketorolac may experience a faster return to work period. This shorter period may equate to less man hours lost. This hypothesis is based on previously demonstrated higher incidents of dose related adverse events.

We anticipate that there will be a lower rate of adverse outcomes by utilizing lower doses of ketorolac. These findings result in multiple benefits to the DoD, service member, and beneficiary. First, by showing a lower rate of adverse outcomes, treating with the lower dose may improve readiness by decreasing lost man hours. Secondly, reducing the amount of adverse effects while maintaining the same level of therapy, patient satisfaction may improve, as well.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

Definitions

1. Acute – onset of symptoms within 30 days on the day of data collection.
2. Musculoskeletal (MSK) – a general term used to described the various forms of pain effecting the musculoskeletal system, for this study. The types of pain included in this definition are undifferentiated muscular, undifferentiated bony, undifferentiated soft tissue, neck, back (to include cervical, thoracic, lumbar, and sacral), shoulder, arm, elbow, forearm, wrist, hand, hip, thigh, knee, leg, ankle, foot and digits).
3. Potential subject – any patient presenting to the WBAMC ED meeting age inclusion criteria with an Emergency Severity Index (ESI) score of 4 or 5 and having a chief complaint of musculoskeletal (MSK) pain, as defined above.
4. Subject – any potential subject meeting aforementioned criteria for enrollment, who met all inclusion criteria, who did not meet any exclusion criteria, who provided informed consent, and signed the Healthcare Information Portability and Accountability Act (HIPAA) Authorization Form.
5. Subject Study Packet –the packet containing documents used to annotate eligibility, acceptance, and consent to participate in the study. Forms included within the packet are the Ketorolac Research Form, Informed Consent Form, HIPAA Authorization Form, and VAS forms (1-3).

Subject Study Number – The randomized number assigned to each subject in order to de-identify data for purpose of protecting Personal Identifiable Information during the reporting of the study's results.

Prescreening / Recruitment Process

During the consent process, the patient will be informed that there is the potential for inadequate pain control while participating in this study. They will be informed that they are entitled to additional pain control medications at any time, as appropriately determined by their provider. See the second to last paragraph of section 5 of the Informed Consent Form. Due to the nature of the study, study subjects requiring additional analgesia prior to the 60-minute re-evaluation will be unenrolled. No further data will be collected once they are unenrolled.

Female potential subjects require a separate further step in order to be officially enrolled as subjects. The following four paragraphs describe the process for enrollment of female subjects. Pregnancy and breast feeding meet exclusion criteria for this study and the following paragraphs describe exactly how investigators will take multiple steps to ensure that only non-pregnant females are enrolled.

As stated above, female potential subjects will be required to provide a urine sample to complete a POC UHCG test. Due to this requirement, their informed consent includes consent to providing a single urine sample for testing. They will be informed that their urine is not required for or used for any other part of the study or data collection.

The POC UHCG is a test performed by WBAMC nurses and it can be performed in triage, usually only taking a few minutes. The result of the POC UHCG is documented by the nurse as positive or negative in the comments section of the T-System™ home screen, indicating either pregnancy or no pregnancy respectively. WBAMC ED uses the QuickVue+® One-Step hCG Combo Test (manufactured by Quidel Corporation). Per manufacturer clinical trials, both the sensitivity and specificity for this test is 99%[25]. Despite the fact that this test is imperfect at detecting pregnancy, it does have a very high sensitivity and specificity. Using this process, investigators are confident that only non-pregnant females will be enrolled in the study.

Specimens collected will not be retained for further use, will be destroyed in accordance with WBAMC lab specimen policy and will not be used for any other purpose unless directed by the attending provider (e. g.: urine culture or urinalysis as ordered by the attending provider).

All POC UHCG results will be communicated with the attending provider (verbally and by being documented in the comments section of the T-System™ home screen) and the attending provider will be responsible for conveying the results to the female potential subject. In the event that the female potential subject is a patient of the PI during the PIs ED shift, the PI with the permission of the attending may also convey the results of the test.

Upon meeting all of the aforementioned criteria for enrollment, providing a signature on the Informed Consent Form and HIPAA Authorization Form, the potential subject will be considered enrolled as a subject for the study.

Randomization and Study Subject Packet Creation

Fully enrolled subjects will be randomized based on a two block randomization generated by the website www.graphpad.com. Randomization will be created so there are two groups (two block randomization), one which will receive 15 mg of intramuscular ketorolac and one which will receive 60 mg of intramuscular ketorolac. Each group (block) will consist of 61 subjects per the power analysis described later in this document and will be assigned a Subject Study Number.

The Subject Study Number will be comprised of a "K" for ketorolac, "15" or "60" designating which dose of ketorolac will be administered and then a specific number reflecting their position within the randomization block (randomization block number). For instance, a Subject Study Number of "K15-30" would signify that this patient was randomized into the ketorolac 15 mg group and the number 30 would reflect both the block to which the patient was randomized and confirm that the patient is indeed in the 15 mg group. Using both "15" or "60" and the randomization block number acts as a checks and balance to ensure that the patient is randomized into the correct group, and that the subject receives the correct randomized dose. Based on the randomization block number it is possible to know into which group the subject was randomized, the dose of ketorolac which will be administered and the order of the patient in the overall randomization. Following randomization, Subject Study Packets will be prepared.

Subject Study Packets will be prepared prior to the data collection (prior to the screening process). These packets will be created using manila envelopes capable of containing all study documents and which can be sealed. The contents of the envelopes will include the (1.) Ketorolac Research Form, (2.) Informed Consent Form (which includes consent for a POC UHCG), (3.) HIPAA Authorization Form, (4.) pretreatment VAS form, and two post-treatment VAS forms. None of the documents utilized or created throughout the study will be entered in to the subjects EHR. The manila packet and all documents contained within it will be annotated with the Subject Study Number (as described above). A description of these forms is listed below.

1. Ketorolac Research Form: this form documents age, gender, pain location, inclusion criteria, exclusion criteria, objective adverse effects, and subjective adverse effects. No PHI or PII will be annotated on this form.
    1. Age will be documented in years only. The actual date of birth will not be documented.
    2. Gender will be documented as "M" for male or "F" for female. Or an appropriate box will be "checked" by the potential subject indicating subject gender.
    3. Pain location will be free text, but will be qualified and isolated to an anatomical region. This will be at the discretion of the investigator. For instance, "heel pain" would be annotated as foot pain, or "calf pain" as leg pain. The anatomical regions designated for the purposes of this research are: (1.) neck pain, (2.) shoulder pain, (3.) arm pain, (4.) elbow pain, (5.) forearm pain, (6.) wrist pain, (7.) hand pain, (8.) hip pain, (9.) thigh pain, (10.) knee pain, (11.) leg pain, (12.) ankle pain, (13.) foot pain or (14.) back pain.
    4. See inclusion and exclusion section in this document for a detailed description of both.
    5. Adverse events which occur due to administration of intramuscular ketorolac will be documented as objective and subjective adverse effects. [Note, "adverse events" is a phrase used to describe adverse events, reactions, and effects to intramuscular ketorolac.] Subjects will be provided a list of known adverse events occurring in greater than 1% of patients during the U.S. Food and Drug Administration (FDA) trials, according to the medical website UpToDate.com. The list of adverse events will be included on the Ketorolac Research Form. Subjects will be advised to circle any of the adverse events that they are experiencing. Each circled adverse event will count as 1 in a binary numbering system (1 indicating an adverse event and 0 indicating no adverse event) for purposes of analysis. Subjects may have more than one adverse event and each event will count as 1 point. The definitions of objective and subjective adverse event are provided below.
        1. Objective adverse events are those identified during reassessment immediately following the initial ketorolac administration, and at the 30 minute and 60 minute re-evaluation intervals. To better facilitate analysis, a list of the most commonly occurring objective adverse events, according to UpToDate.com, will be provided for the investigator to choose from. This list will be included on the Ketorolac Research Form. Objective adverse events are any (1.) subjective events (signs or symptoms) which can be validated or observed by study investigators (such as diaphoresis), (2.) are obvious to the investigator, but perhaps not the patient (mild facial swelling or rash) or (3.) abnormal vital signs. Blood pressure and heart rate measurements will be taken at the 30 minute and 60 minute intervals. Any deviation of blood pressure or heart rate which would meet exclusion criteria for this study would prompt immediate notification of the attending provider and the patient would be excluded from the study.
        2. Subjective adverse events are any symptoms conveyed by the subject, but are not measureable, observable or verifiable by the investigator. To better facilitate analysis, a list of the most commonly occurring subjective adverse events, according to UpToDate.com, will be provided to the study subject to choose from. Examples of subjective adverse events may include dizziness, light headedness or nausea (this is not an exhaustive list of subjective adverse events).
2. Informed Consent Form: this document describes important details and purpose of the research, risks, benefits, alternatives, use of PHI and PII, obtains consent from female potential subjects for a POC UHCG and obtains official consent in the form of the subject's signature. This form will be explained in detail with the patient to ensure their complete and total understanding. The patient will be given as much time as possible to contemplate the decision to enroll as a subject in this study. However, once roomed in the ED, the patient will no longer be eligible to enroll. The patient will be given the opportunity to ask as many questions as possible prior to obtaining signature and will be informed that they have the right to withdraw from the study at any point.
3. HIPAA Authorization Form: signature of this document authorizes investigators use of the subject' s protected health information (PHI) and personally identifiable information (PII) responsibly, securely and only for the purposes of this study. PHI and PII will be explained in detail to the patient and all questions will be honored. Should the patient decline to sign this document, they will be excluded from the study.
    1. PHI: The only protected health information used for this study will be the (1.) chief complaint and (2.) vital signs. A review of systems (ROS) will be used for inclusion and exclusion purposes of this study, but the EHR will not be accessed for this information and this information will not be documented on any media. A detailed description of the ROS is provided later in this application.
    2. PII: The only PII used for this study will be the (1.) subject name, (2.) age (in years-not date of birth), (3.) medical record number (MRN) and (4.) gender.

4. VAS forms (pretreatment and post-treatment): these are single page forms with a 0-100 mm VAS. Four separate VAS forms will be included in the Subject Study Packet and will be used to assess the subject's pain prior to administration of ketorolac, and at the 30 and 60 minute intervals after ketorolac administration. A fourth form will be included in the event that the patient completes the VAS incorrectly. The subject in each instance and on separate forms, will be asked to mark a horizontal line on the 0-100 mm continuum indicating their pre-treatment level of pain and their pain level post-treatment at the 30 minute and 60 minute intervals. Three separate forms are utilized to control for response bias. The Subject Study Number will also be included on the document, but otherwise no other information will be contained on the VAS forms.

With the exception of the actual data collection phase of this study, the Subject Study Packets will be secured in a locker within the WBAMC ED which can only be accessed by the investigators. The locker will be padlocked and access to the room containing the locker requires key-card access and cypher lock access (a code entered into the automated door lock prior to being able to open it). The Subject Study Packets will remain in this location throughout the data collection phase, but will then be transferred securely to WBAMC room 10015 (the emergency medicine physician assistant resident room) for at least three years following completion of the study (for auditing purposes). Upon completion of the three year, post-study period, the documents will be destroyed in accordance with WBAMC local policy and procedure for destruction of such documents.

A hard-copy master key will be created to bridge the study subjects' de-identified Ketorolac Research Forms with the excel document which will be used to compile all of the study data. The master key will annotate the (1.) Subject Study Number., (2.) name and (3.) MRN. The information which the master key holds will be collected only after the patient has been consented and enrolled in to the study but prior to administration of the medication. This document will be maintained for the sole purpose of identifying subjects for the duration of data collection and analysis period. This document will be a hard copy document on standard sized printer paper within a document sized manila envelope. It will be secured by the investigator in the same manner as the other documents.

Medication Administration

The primary investigator (PI) will maintain a resident-status through the Army-Baylor Doctor of Science Physician Assistant Studies Program for the entire research period of this study. The PI is a licensed physician assistant-certified and can under normal circumstances prescribe medication without approval by an attending physician. However due to the PI resident-status, all final treatment decisions (to include the ketorolac dosing used for this study) must be approved by a WBAMC ED attending provider.

For purposes of this study, the attending provider is usually a physician, but may be a physician assistant or nurse practitioner, and is the provider responsible for the subject's medical care at the time of data collection. Therefore, the attending provider is not a single individual. The PI may have a different attending provider for each shift or the attending may vary (being more than one individual) within one specific ED shift. Again, the attending provider is the final medical authority for every subject and it is the attending provider who will ultimately approve or disapprove ketorolac dosing regimens as they pertain to this study.

For instance, the PI may enroll and randomize a patient to the 15 mg ketorolac group. The PI will communicate this to the attending provider. However, the attending provider may reject the 15 mg dose and opt for a lower dose, higher dose or no ketorolac dose at all. For this reason, the inclusion and exclusion criteria for this study will document attending provider approval of the dosing regimen to which the patient is randomized prior to administration of the ketorolac.

The Regional Health Command Central (RHC-C) Human Research Protection Program was consulted on this issue specifically. Their guidance was that, for the purposes of this study, the attending physicians are not human subjects research in this study and do not require formal written consent to signify approval of the randomized ketorolac dose. However, they recommended that the PI obtain concurrence with the dose from the attending provider. The investigators for this study will have the attending provider sign the Ketorolac Research Form signifying their concurrence with the randomized dose.

Study participants whose randomized dosing regimens are rejected by the attending provider will be excluded from the study. Again, attending provider concurrence with the randomized ketorolac dosing utilized in this study will be documented on the Ketorolac Research Form and is reviewed in the inclusion and exclusion portion of this application.

Prior to administration of ketorolac, a review of systems (ROS) will be performed with each patient to ensure that the subject has no medical history or other acute medical problems which would meet exclusion criteria for this study. However, this information will not be documented on any forms and will not be accessed through the EHR. The ROS is an anatomic or physiologic systems based detailed

interview with the patient to discuss their overall health and to identify any other medical issues that may or may not be connected with the patient's reason for ED visit.

The ROS used for this study is located within this application and will be located in the appendix of the manuscript when this study is complete. The study investigators' ROS may be separate from the actual attending provider ROS. The attending provider will perform their own ROS based on standard medical history taking. However, the ROS performed by the investigators for the purpose of this study will be used to discover any other medical issue or issues which may meet inclusion or exclusion criteria. If deemed pertinent to patient care, information obtained by performing the investigator ROS will be communicated verbally to the attending provider, so that they are aware that the patient may require evaluation for medical issues beyond an acute MSK injury or pain.

Ketorolac will be prepared for IM injection by the nursing staff assigned to the patient once the following have taken place:

1. Study subject has granted consent

2. Pregnancy is excluded

3. Breast feeding is excluded

4. Inclusion criteria are met

5. None of the exclusion criteria are met

6. The ROS is complete

7. The attending provider agrees to the randomized dose and formally prescribes the randomized dose of ketorolac through the EHR

8. Ketorolac will then be prepared for IM injection by the nursing staff assigned to the patient

All appropriate provider and nursing policies, safeguards and regulations governing the preparation and administration of parenteral medication within the WBAMC ED will be followed and standard of care for the injection of ketorolac will not be altered, omitted or deviated from industry, ethical, moral or hospital standards. The investigators will not have any part in preparation or administration of the ketorolac-this will be completely handled by WBAMC ED nursing staff and the order for the ketorolac will have already been approved and prescribed by the WBAMC attending ED provider through the EHR.

As the medication is prepared for administration, the investigator will educate the subject on the use of the VAS and annotate their pre-treatment pain score on the VAS form. For the purposes of this study, the VAS is a validated tool that will be used to objectively measure the subject's response to ketorolac.

The subject will then be injected intramuscularly with the dose of ketorolac randomized to the patient based on the Subject Study Number assigned to the randomized packet, which was assigned to that subject. Again, all appropriate provider and nursing policies, safeguards and regulations governing the preparation and administration of parenteral medication within the WBAMC ED will be followed and standard of care for the injection of ketorolac will not be altered, omitted or deviated from industry, ethical, moral or hospital standards.

Following the administration of ketorolac and at the 30 and 60 minute intervals, VAS scores will be recorded, the patient will be assessed for adverse effects (objective and subjective) and blood pressure and heart rate measurements will be taken. At the conclusion of the 60 minute period and documentation of the VAS and any adverse effects, the data collection phase will be considered complete. The subject will be notified that the study has concluded. The attending provider will then continue with evaluation, treatment, and disposition, as indicated.

As outlined during the consent process, additional analgesia will be available during the course of the study. The decision to provide additional analgesia will be made by the attending provider in consideration of the study subject's clinical scenario. Study subjects who receive additional analgesia will be unenrolled from the study at the time of administration of the additional analgesia.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

Primary Outcome Variable Data:
The primary outcomes will be a clinically significant reduction in the numeric rating using the visual analog scale at 30 and 60 minutes from medication administration and compared to the pre-treatment VAS.

The primary outcome variables will be the change in subjective pain reported by patients using a VAS. The VAS is a validated measurement instrument used to record subjective reports of pain, or other subjective conditions. There are several different VAS constructs but this study will utilize a single horizontal line measuring 0-100 mm with short vertical marks as borders at each edge. All investigators will independently measure the VAS line to ensure that the printed line on the VAS form measures exactly 100 mm. The phrase "No pain" will be placed to the left of the 0 mm mark and the phrase "Severe Pain" will be placed to the right of the 100 mm mark. There will be no numerical or other incremental marks along, within or above the scale. The study subject will be instructed on the use of the scale prior to having their pain assessed. They will be informed that the scale measures from left to right, least to greatest level of pain. To annotate their pain level, they will be instructed to signify their level of pain on a scale of "0 mm or no pain at all" to "100 mm or Severe Pain" by making a single vertical mark through the horizontal VAS line on the document. If they do not make a vertical mark (circle, forward slash, backward slash, or otherwise), it is not through the horizontal VAS line, or illegible the investigator will retrain the patient on how to complete the form and a new form will be provided for the patient. An extra VAS is included in each Subject Study Packet for this purpose. Once completed, the forms will be returned to the subject study packet.

To measure the subject's reported level of pain on the VAS, the investigator will measure from the beginning of the scale to the vertical mark drawn by the subject. The "0 mark" on the metric tape measure will be aligned with the "0 mark" on the VAS form and the millimeters from the "0 mark" to the vertical line representing the subject's pain will be tallied. This distance will be annotated next to the scale for ease of reference. All VAS measurements will be completed and documented in the same manner for the 30 and 60 minute intervals. This study will use a previously validated measure of a 13 mm change in VAS to determine the minimum clinical significant difference (MCSD). (REF). Please refer to the statistical analysis portion of this document for more information about how this data will be used.

VAS measurements will not be taken during the data collection phase of this study. Only after data collection has been completed for the entire study and all VAS forms have been completed for all study subjects will the investigators actually measure and record the VAS scores. The purpose of not measuring the VAS at the time of data collection is to reduce research bias. Measurement of all VAS forms will take place at a predetermined time and place for both investigators (PI and AI). During the VAS measurement process, all investigators involved with the research must agree upon the measurement obtained. If, there is a discrepancy with the measurement process or measurement obtained, the VAS will not be used and the patient will be excluded from the study. The methodology for measuring the VAS will be based on prior literature explaining the process, in order to reduce inaccuracies [26].

Secondary Outcome Variable Data.
The secondary outcome variables will be the number of subjects experiencing adverse events (both objective and subjective). This data will be provided by the subjects or observed, measured or verified by the investigators and will be documented on the adverse events section of the Ketorolac Research Form. Adverse events will be documented as objective and subjective adverse events. Subjects will be provided a list of the most common adverse events based on the medical website UpToDate.com. This list will be included on the Ketorolac Research Form. Subjects will be advised to circle any of the adverse events that they are experiencing. Each circled adverse event will count as 1 in a binary numbering system (1 indicating an adverse event and 0 indicating no adverse event) for purposes of analysis. Subjects may have more than one adverse event and each event will count as 1 point. The definitions of objective and subjective adverse event are provided below.

1. **Objective adverse events**
    1. Objective adverse events will be described based on objective findings found during reassessment immediately following the initial ketorolac administration, and at the 30 minute and 60 minute re-evaluation intervals. Objective adverse events are any (1.) subjective events (signs or symptoms) which can be validated or observed by study investigators (such as rash or obvious dyspnea), (2.) are obvious to the investigator, but perhaps not the patient (mild facial swelling or rash) or (3.) abnormal vital signs. Blood pressure and heart rate measurements will be taken at the 30 minute and 60 minute intervals. Any deviation of blood pressure or heart rate which would meet exclusion criteria for this study would prompt immediate notification of the attending provider and the patient would be excluded from the study.
2. **Subjective adverse events**
    1. Subjective adverse events are any symptoms conveyed by the subject, but are not measureable, observable or verifiable by the investigator. To better facilitate analysis, a list of the most common subjective adverse events, according to UpToDate.com, will be provided to the study subject to choose from. Examples of subjective adverse events may include dizziness, light headedness or nausea (this is not an exhaustive list of subjective

adverse events). Study investigators will review, confer, agree upon and categorize the adverse events (based on the subjective report) prior to submitting them to the statistician for analysis.

Descriptive Statistics Data.
Descriptive statistics data will be gathered to find correlation between subject demographics (age and gender) and location and duration of pain. These data will be obtained on the Ketorolac Research Form which is completed by the subject and will be included as descriptive statistics only. The data may or may not be analyzed for statistical significance, this will be at the discretion of the statistician. Furthermore, data pertaining to subjects requiring analgesia beyond the ketorolac used for this study, will also be collected for descriptive purposes only. Furthermore, data pertaining to subjects requiring analgesia beyond ketorolac, will be collected for descriptive purposes only. The data will be collected on the Ketorolac Data Collection Workbook, along with the other data.

At the completion of the entire data collection period for the entire study, VAS measurements will be obtained based on the methodology above and all data pertaining to the primary outcome (VAS scores), secondary outcome (adverse events) and descriptive statistics (from the Ketorolac Research Form) will be transcribed on to a Microsoft Excel work sheet. Any PHI or PII at this point will be de-identified and only the Subject Study Number will be used for identification. All paper documents will be secured in a manner previously described. The Excel worksheet is located on the PIs government issued common-access-card protected laptop. Access to this laptop requires both a common-access-card and a personal identification number (PIN) assigned to that specific common-access-card. The worksheet will therefore be highly secure and saved to the hard drive of the PIs laptop. The hard drive on the computer can only be accessed by the PI (as previously discussed) and network system administrators with permission. The AI for this research may also have a copy of the de-identified data, however, the data will be stored and secured in the exact same manner as the PI (common-access-card and PIN protected). All measures will be taken to protect the information of the study, however no PHI or PII will be stored on the Microsoft Excel work sheet.

10.3 At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

(•) Yes ( ) No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance.

The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force

***MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS.**

***MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.**

Are you an MHS workforce member?

(•) Yes, I am an MHS workforce member
( ) No, I am not an MHS workforce member

Are you an MHS business associate?

( ) Yes, I am an MHS business associate
(•) No, I am not an MHS business associate

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**DHA.PrivacyBoard@mail.mil**)

- ○ Yes, then complete the questions below according to the data consult
- ◉ No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

- ☐ Talking with MHS health care providers or MHS health plans about specific research participants
- ☐ Obtaining MHS hard copy records specific to research participants
- ☑ Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

- ☐ Data Extract
- ☑ Access

10.8 Do you intend to request de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

○ Yes ◉ No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
PHI Systems:

	MHS Information System	Requesting Data
	AHLTA	No
	CHCS	No

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added	

De-Identified Data & Other Systems:

Information System	Requesting Data
Other MHS System (May include PII and/or PHI) List other system here: T Systems (to identify potential subjects during prescreening process)	: No

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- (•) Yes, will merge data
- ( ) No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.

If you will merge data, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Data Element(s)	MHS	Non-MHS Systems	MHS Hard Copies
1. Names	☑	☐	☐
2. Postal address with only town, city, state and zip code	☐	☐	☐
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	☐	☐	☐
4. Dates including all elements (except year)	☑	☐	☐

directly related to an individual, including birth date, admission date, discharge date, and date of death			
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐	☐
6. Telephone numbers	☐	☐	☐
7. Fax numbers	☐	☐	☐
8. Electronic mail addresses	☐	☐	☐
9. Social Security numbers (SSNs)	☐	☐	☐
10. Medical record numbers	☑	☐	☐
11. Health plan beneficiary numbers	☐	☐	☐
12. Account numbers	☐	☐	☐
13. Certificate/license numbers	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐	☐
	☐	☐	☐

19. Full-face photographic images and any comparable images			
20. Any other unique identifying number, characteristic, or code (Diagnosis, DEERS ID, EDI-PI, Rank)	☐	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ○ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ◉ No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 Have you completed and uploaded an appropriate HIPAA document (i.e. HIPAA Authorization will be obtained or Waiver/alteration of HIPAA Authorization is being requested)?

- ◉ Yes
- ○ No
- ○ N/A

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

As outlined in the procedures section, data acquired will initially be obtained by the investigator via T-system™ home screen during the pre-screening process. Data collection will occur from the time the subject provides informed consent through the conclusion of the data collection period. As the primary outcome, subjective pain level will be obtained upon administration of intramuscular ketorolac then 30 and 60 minutes after administration. As the secondary outcome, adverse effects will be assessed for at 30 and 60 minutes after administration of intramuscular ketorolac. Descriptive statistics will also be obtained on the Ketorolac Research Form after informed consent is obtained.

The subjective pain levels will be annotated on the three VAS forms. The descriptive data and adverse effects will be annotated on the WBAMC Ketorolac Research Form. These forms will be placed within the document envelopes for the duration of the study. At the end of each study day, the data from each

study subject will be transcribed on to the Excel document on the PIs government issued laptop. The laptop will physically be in the PIs possession for the duration of the study.

The only human biological specimen which will be obtained will be urine. It will be used for a POC UHCG test in order to assess for pregnancy. These specimens will be obtained, handled, processed, and destroyed in accordance with WBAMC ED and hospital policies. The results of the POC UHCG will be reported verbally to the attending and/or via the T-System comments section in EHR, which does not require access to the subject's individual EHR for their specific ED encounter.

The subject's EHR will not be accessed for any reason for the purposes of this research. All PHI or PII will be gathered on paper and will be provided voluntarily by the study subject. This information will be de-identified after consent is obtained and only the study subject randomized number will be used for identification.

All paper documents will be held in a locked locker in the WBAMC ED for the duration of the data collection period, analysis period, and as the manuscript is produced. Upon completion of the manuscript, the documents will be securely transferred to the WBAMC room 10015 and secured in a locked cabinet for a period of up two years. Upon completion of the three year, post-study period, the documents will be destroyed in accordance with WBAMC sensitive document disposal policies.

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens /data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

N/A

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

The primary outcome will be the difference in VAS from baseline to 30 minutes and from baseline to 60 minutes. Our research hypothesis is that the measured pain relief using 15mg of intramuscular ketorolac will be non-inferior to the measured pain relief using 60mg of intramuscular ketorolac. Whereas in a clinical study where the research hypothesis is that one treatment, say drug A, is demonstrated to have a better (improved pain relief) outcome than the second treatment, say drug B, we are hypothesizing that smaller dose drug is not inferior in terms of pain relief than the higher drug dose. We fully suspect that the higher drug dose will have a better average outcome, but the question of interest is, is the outcome for the lower dose drug non-inferior to that of the higher drug dose. The analysis used in this study is a non-inferiority test. This hypothesis can be tested using a variety of methods that involve the construction of one-sided confidence interval or one-sided, two-sample equal-variance t-test with alpha of 0.05. In both methods, the power and sample size can be computed.

11.2 Sample Size:

n=122 (This assumes 10% dropouts or withdrawals from our required n=110)

11.3 Total number of subjects requested (including records and specimens):

122

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm

15mg IM ketorolac arm = 61 subjects
60mg IM ketorolac arm = 61 subjects

11.5 Please provide a justification for your sample size

In this study, we assume that we are comparing the mean VAS between the 2 Groups, and the margin of non-inferiority is -13 mm. The actual difference between the means is assumed to be 0 and the standard deviation is assumed to be 27 for the 2 Groups (estimated from the Motov manuscript). Group sample sizes of 55 and 55 achieve 80% power to detect non-inferiority using a one-sided, two-sample equal-variance t-test with alpha of 0.05. The sample size per arm was increased from 55 to 61 to account for an anticipated 10% dropout or withdrawal of subjects (5.5 subjects was rounded to 6 subjects).

11.6 Data Analysis Plan: Complete description: Background, Objectives, Design, Step by Step how the project is going to be done, Data analysis plan:

To test for non-inferiority of dose 15mg to dose 60 mg using the VAS pain score, the analysis to be used is called an interval test. The hypothesis will be tested using the construction of one-sided confidence intervals or one-sided, two-sample equal-variance t-test with alpha of 0.05. To test that the lower dose has less adverse effects, we will use the one-sided z-test for testing two independent proportions. All tests will be conducted at the 0.05 level of significance.

12.0 Participant Information

12.1 Subject Population:

Patients considered for this study will include adults aged 18 to 55 years who present to the ED for management of acute musculoskeletal pain with an intensity of 20 or greater on a standard 100mm visual analog scale and who would routinely be treated with intramuscular ketorolac in the WBAMC ED as determined by the attending emergency room medical provider. Subjects must also not be pregnant or lactating to be eligible for enrollment.

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- [ ] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [ ] 55-64
- [ ] 65-74
- [ ] 75+

18 - 55

12.3 Gender:

- [x] Male
- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [ ] Students
- [ ] Employees - Civilian
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen
- [ ] Active Duty Military Personnel
- [ ] Wounded Warriors
- [ ] Economically Disadvantaged Persons
- [ ] Educationally Disadvantaged Persons
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

12.5 Inclusion Criteria:

Order Number	Criteria
1	Age 18-55 years of age Study subject is one of the following; DoD service member, DoD beneficiary, or Veteran Affairs beneficiary ESI 4 or 5 Presenting to WBAMC ED for management of musculoskeletal pain (i.e., general muscular, neck, back, shoulder, arm, forearm, elbow, wrist, finger, hip, knee, thigh, leg, ankle, foot or digits) Pain intensity of 20 mm or greater on a standard 100 mm visual analog scale Pain duration less than 30 days Attending provider concurs with intramuscular ketorolac administration for analgesia

12.6 Exclusion Criteria:

Order Number	Criteria
	Patients weighing less than 50 kg (110 lbs) Patients younger than 18 or older than 55 years Pregnant or breast feeding

1	History of: confirmed, unconfirmed, known, unknown, or suspected peptic ulcer disease, intestinal hemorrhage, renal insufficiency, hepatic insufficiency, cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, dark stools, bright red blood per rectum, hemoptysis, easy bruising, or high risk of bleeding Unable to confidently convey or unknown medical history Allergy or hypersensitivity to nonsteroidal anti-inflammatory drugs or Aspirin Systolic blood pressure <90 or >180 mmHg; pulse rate <50 or >150 beats/min Any over-the-counter or prescribed opioid and/or non-opioid analgesic medication (oral, per rectum, topical or parenteral) taken within 12 hours of ED presentation Advised by any medical provider to not receive non-steroidal anti-inflammatory drugs (NSAIDs) for any reason Pain duration greater than 30 days Refusal to remain in the WBAMC ED for up to 60 minutes after injection of ketorolac Patients currently taking anticoagulant medications Concurrent use of medications which are contraindicated with concomitant NSAID use. These drugs include aspirin, probenecid and pentoxifylline

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

Potential subjects will be verbally recruited for participation in the study utilizing a preformatted verbal synopsis. In a private setting (ED room or ED bay) at the WBAMC ED 5005 N. Piedras Street El Paso, TX 79920, potential subjects will be notified of their initial eligibility and provided with a verbal synopsis of the study to include objectives, benefits, and risks. This is not a formal consent process but will provide potential subjects with a basic overview of the study and obtain their verbal willingness to pursue participation further. Potential subjects at this point may agree with participation in the study, decline participation or request time to consider participation. Potential subjects who decline participation will be thanked for their time and escorted back to the WBAMC ED waiting room. Potential subjects who request time to consider participation will be given until they are roomed within the WBAMC to make a decision. This time frame is dependent on WBAMC ED wait times and may be minutes or may be hours. Should a potential subject decide to participate after consideration, their request will be honored: as long as they have not been roomed or their participation would interfere with the study process or randomization at that time. No PHI or PII will be documented on these potential subjects.

13.2 Compensation for Participation:

Patients will not be compensated for participation in this study.

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

The investigators will monitor the WBAMC ED electronic health record (EHR) T-System™ (manufactured by T-System™ Incorporated) for all patients presenting to the WBAMC ED with an Emergency Severity Index (ESI) score of 4 or 5 meeting inclusion criteria age and having a chief complaint of musculoskeletal (MSK) pain. T-System™ is the ED EHR used to electronically document all aspects of patient medical care from ED registration through discharge. However, individual patient ED medical records will not be accessed for the purposes of this research. Only the T-System™ "Home" screen will be accessed and viewed when prescreening patients for this study, and the remainder of this study will not require access to any other part of the patient ED EHR. The T-System™ home screen does not provide detailed patient medical information, such as a patient history, treatment or diagnosis. It does provide the viewer with the following:

1. Area (the general area or section of the WBAMC ED where the patient is physically located-this could be either in the "main ED" or in the "fast track section")

2. Room (the actual ED room number where the patient is located)

3. Patient name

4. Chief complaint

5. Triage category (ESI category)

6. Nurse(s) name(s) assigned to the patient

7. Physician(s) or provider(s) name(s) assigned to the patient

8. Comments

9. Disposition of the patient (admit, discharge, etc.)

There are other categories on the screen for vital signs and orders, but these do not display specific vital signs or specific orders, unless accessed by the user through "clicking" on these categories. The vital signs category will be accessed to determine if the patient's heart rate, temperature and blood pressure meet inclusion criteria. However, for the purposes of this study-no other protected health information (PHI) or personally identifiable information (PII) will be accessed, viewed or used. Again, the T-System™ home screen will be used only to determine the age of the potential subject, their ESI category and their chief complaint (and vital signs, but this is during the screening process). This data will be used to prescreen and identify any potential subjects for this study and to initiate the recruitment process. The data identified during this process is not recorded anywhere. Patients meeting the three above prescreening criteria will be considered potential subjects.

When prescreening T-System™ for a chief complaint of MSK pain, it should be known that MSK pain is a blanket term which encompasses many different types of injuries and/or pain. For completeness, a definition of MSK pain, as pertinent to this study, is located in the definitions section of this document. However, for brevity, the term MSK pain will be utilized throughout the remainder of this document.

The ESI is a standardized ED triage algorithm utilized nationwide to stratify patient triage acuity. ESI scores range from 1 to 5, with 1 being the most emergent medical conditions and 5 being the least emergent medical conditions. For an example, a patient with an ESI score of 1 may have severe trauma or present in cardiac arrest, whereas a patient with an ESI score of 5 may only require a medication refill or suture removal. For the purpose of this study, only ESI scores of 4 or 5 will be included. The rationale for excluding ESI categories 1-3 is that ESI categories of 4 and 5 are unlikely to have been the result of, or develop into a serious injury or illness during a patient's ED stay. ESI categories 1-3 may require extensive laboratory, imaging and/or opiate pharmacotherapy during their ED stay, which may confound study results. Whereas, a patient presenting with an acute MSK injury or pain and an ESI category of 4 or 5 will have a greater likelihood of being treated with a single non-opioid analgesic, such as ketorolac. Therefore, by choosing ESI categories 4 or 5, our study makes it unlikely that the patient has a serious medical process (or that a serious medical issue will develop during their ED stay) and/or will require opiate analgesics during their ED stay. Also, selecting for ESI categories 4 or 5 increases the likelihood of ketorolac being the only analgesic required during their ED stay. A complete explanation of ESI scores is beyond the scope of this document; more information can be obtained at https://www.ahrq.gov[24]. Subjects who meet the age inclusion criteria, have an ESI score of 4 or 5 and a chief complaint of MSK pain will be considered prescreened as potential subjects for enrollment in this study.

Note: the primary investigator will be conducting the research during time allocated for research. He will not be a part of the care team for the potential study subjects.

13.4 Consent Process:

Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

Potential subjects will then be verbally recruited for participation in the study. In a private setting (ED room or ED bay), potential subjects will be notified of their initial eligibility and provided with a verbal synopsis of the study. The verbal recruited will be performed by the investigator reading the scripted verbal synopsis document, which is attached as an appendix to this protocol submission. This will provide potential subjects with a basic overview of the study and obtain their verbal willingness to pursue participation further. Potential subjects at this point may agree with participation in the study, decline participation or request time to consider participation. Potential subjects who decline participation will be thanked for their time and escorted back to the WBAMC ED waiting room.

Potential subjects who request time to consider participation will be given until they are roomed within the WBAMC to make a decision. This time frame is dependent on WBAMC ED wait times and may be minutes or may be hours. Should a potential subject decide to participate after consideration, their request will be honored: as long as they have not been roomed. No PHI or PII will be documented on these potential subjects.

Potential subjects who grant verbal willingness to participate in this study will then be formally consented. The consent process includes a complete description of the study to include objectives of the study, benefits to the DoD, process, subject time commitment, risks, benefits, alternatives and documentation to be completed by subject. Only after the consent process is described, all of the inclusion criteria are met and none of the exclusion criteria are met, will potential subjects be fully screened. This includes females being screened for pregnancy using a point-of-care (POC) urine human chorionic gonadotropin (UHCG) test (urine pregnancy test). Additionally, to complete enrollment in to the study, subjects will be asked to sign the HIPAA Authorization Form. The HIPAA Authorization Form authorizes investigators access to protected health information (PHI) and Personally Identifiable Information (PII) for purposes only pertaining to this study.

Named investigators on this protocol will conduct the consent process for all subjects enrolled in this study.

Potential subjects who grant verbal willingness and permission to participate in this study will then be consented. The consent process includes a complete description of the study to include objectives of the study, benefits to the DoD, process, subject time commitment, risks, benefits, alternatives and documentation. Only after the formal consent process is described, all of the inclusion criteria are met and none of the exclusion criteria are met, will potential subjects be officially consented using the Informed Consent Form attached with this protocol submission.

Female potential subjects will be consented for a point-of-care (POC) urine human chorionic gonadotropin (UHCG) test (urine pregnancy test).

Upon meeting all of the aforementioned criteria for enrollment, providing a signature on the Informed Consent Form and HIPAA Authorization Form, the potential subject will be considered enrolled as a subject for the study.

13.5

DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

- (•) N/A
- ( ) Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Withdrawal from participation in this study will not cause any undue harm or additional risk to the subject. If the subject wishes to withdraw from the study, they need only to verbally declare their withdrawal from participation. The subject will be informed that their rights for medical treatment will not be impacted in the case of study withdrawal. The patient may be allowed to withdraw at any point throughout the study period and all PHI, PII and data collected at that time will be destroyed in accordance with WBAMC sensitive document disposal policies. Withdrawal or exclusion will be documented on a separate document for record purposes and no PHI or PII will be retained.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Note: the risks associated with Ketorolac have been demonstrated to increase with dosage. The risks are listed and discussed below. Separately, due to the risks of the medication in general, the treating provider will be required to concur with the medication and dosage regimen in order for the patient to be enrolled in the study. This is outlined in the inclusion and exclusion criteria.

Non-steroidal anti-inflammatory drugs, such as ketorolac, have the following potential adverse effects: gastrointestinal hemorrhage, nausea, vomiting, dyspepsia, dizziness or lightheadedness, and somnolence. 1 Gastrointestinal hemorrhage is the most concerning because it also appears to be dose-dependent. The risk for gastrointestinal bleeding is highest for ketorolac out of all of the nonsteroidal anti-inflammatory drugs.4 Additionally, single doses of parenteral ketorolac have been demonstrated to interfere with platelet function by prolonging bleeding time, inhibiting platelet aggregation, and reducing platelet thromboxane production.5–7 Likewise, single doses of ketorolac at 15 mg and 30 mg intravenously and 60 mg intramuscularly have been shown to worsen hemorrhage in postoperative patients.8,9

There is a very low risk for harm with participation in this study as the medication is being administered as recommended by the package insert and as recommended by the Food and Drug Administration. Furthermore, patients who are at increased risk for these adverse events will not be enrolled in the study, based on questions asked using the inclusion and exclusion criteria during the consent process. Ketorolac has the following known adverse events with applicable percent of patients who experience these effects: headache (17%), gastrointestinal pain (13%), dyspepsia (12%), nausea (12%), edema (4%), hypertension, dizziness (7%), drowsiness (6%), diaphoresis, pruritus, skin rash, diarrhea (7%), constipation, flatulence, gastrointestinal fullness, gastrointestinal hemorrhage, gastrointestinal perforation, gastrointestinal ulcer, heartburn, stomatitis, vomiting, anemia, prolonged bleeding time, purpura, increased liver enzymes, pain at injection site (2%), tinnitus, and renal function abnormality[19].

Additionally, there is a risk that the study subjects receiving the 15 mg dose will have inadequate pain control.

There is also the risk of accidental disclosure of protected health information (PHI) or personally identifiable information (PII). However, name and MRN will only be listed on the Master Key. The remainder of the research data will only have the Study Subject Number.

There are specific risks to pregnant and breastfeeding women. There is an FDA boxed warning that ketorolac is contraindicated in labor and delivery due to the potential to inhibit uterine contractions and adverse effects on fetal circulation. Additionally, ketorolac has a pregnancy risk factor of C. In this category, risk to the mother and fetus cannot be ruled out[24].

14.2
Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

The only intervention which will be provided for the conduct of this study is administration of intramuscular ketorolac at either a 15 mg or 60 mg dose. Ketorolac is a commonly used NSAID in the emergency department[17]. There are a number of well-known potential side effects and contraindications to its use[19]. We have outlined specific exclusion criteria to minimize harm and eliminate harm where possible.

During the pre-screening phase, patients with an ESI of 1-3 will be excluded. These patients are excluded because, by definition, their medical process may require multiple medical resources to evaluate and treat[23]. Due to this complexity, there is higher likelihood that patients with an ESI of 1-3 will have underlying disease which may preclude the use of ketorolac. Additionally, during this prescreening process, patients with a systolic blood pressure less than 90 or greater than 180 mmHg and / or a pulse rate less than 50 or greater than 150 beats/min will be excluded. We have set these ranges as exclusion criteria as these values indicate that a more serious underlying pathologic process or multiple underlying pathologic processes are occurring, which could result in the patient requiring interventions beyond a single dose of ketorolac.

During the recruitment and consenting phases, patients will be thoroughly assessed for eligibility to participate in the study using our previously identified inclusion and exclusion criteria. This assessment has been developed with the subject's wellbeing and the greatest possible risk reduction in mind. These criteria were developed after careful analysis of known and potential adverse events and the contraindications, as outlined by the FDA[19]. These criteria are discussed in depth below:

1. We have outlined several specific criteria for women. First, all women will be required to provide a POC UHCG to ensure that they are not pregnant. Those that decline to or cannot provide a urine sample will be excluded. Additionally, women who are pregnant or breastfeeding will be excluded due to the pregnancy risk factor category C and because it is known that ketorolac crosses into breast milk. These criteria were developed to ensure that the risk of ketorolac administration to a pregnant or breast feeding subject is all but eliminated.

2. For all study subjects, there are exclusion criteria related to specific processes which are known to be exacerbated or caused by the use of ketorolac. These include known, unknown, or suspected allergy or hypersensitivity to NSAIDS, peptic ulcer disease, intestinal hemorrhage, renal or hepatic insufficiency, suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, dark stools, bright red blood per rectum, hemoptysis, easy bruising, or high risk of bleeding. Additionally, potential subjects will be excluded if they have ever been advised by any medical provider to not receive non-steroidal anti-inflammatory drugs (NSAIDs) for any reason.

3. Due to the increased risk of adverse effects with higher doses of NSAIDS, patients will be excluded who have used over-the-counter or prescribed NSAID analgesic medication (oral, per

rectum, topical or parenteral) taken within 12 hours of ED presentation. This ensures that study subjects are not provided with NSAID doses above what is recommended.

4. Potential study subjects will be excluded who have any other medical concern identified either through patient history or through the review of systems. This criteria is set as it is the study's aim to evaluate the efficacy of intramuscular ketorolac for pain management, alone. It is not the intent of the investigators to withhold or prevent a complete evaluation and therapy for any medical condition identified during the study period.

5. Finally, potential subjects will be excluded who are unable to confidently convey or report unknown medical history. This prevents the administration of ketorolac in subjects with possible undiagnosed disease.

Separate from the stated exclusion criteria, the risks of administration of the intramuscular ketorolac have been considered in the study's design. As such, all current policies and procedures for the administration of intramuscular medications, as outlined by the Joint Commission, WBAMC, and the WBAMC ED, will be followed.

The data management and methodology for this study mitigates confidentiality risks by de-identifying all subject data documented for the purposes of this study. Subjects will be assigned a Subject Study Number for the data collection and subsequent reporting and building of the final study report.

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

Study subjects will not be identified by their name, social security number, or medical records number (MRN) for the production of the final manuscript, poster, or any publication of the findings of this research. The master key used to identify study subjects will be maintained by the investigator for the duration of the study then destroyed once all data has been transferred from the Ketorolac Research Forms to the excel worksheet. All reportable data will be de-identified and collected on the Ketorolac Research Form and the VAS forms. The documents will be held in a locked locker in the WBAMC ED for the duration of the data collection period, analysis period, and as the manuscript is produced. Upon completion of the manuscript, the documents will be securely transferred to the WBAMC room 10015 and secured in a locked cabinet for a period of up two years. Upon completion of the two-year post-study period, the documents will be destroyed in accordance with WBAMC sensitive document disposal policies.

All data used for analysis will be compiled using Microsoft Excel into a table for ease of reporting. This, password protected, electronic document will be created and stored on a U.S. government issued laptop authorized to created and hold PHI and PII. This laptop is individually issued to the PI, CPT Nathaniel J. Turner, and he is the only person who will have access.

If information must be shared between the investigators or personnel involved in the study (such as statisticians or the WBAMC Department of Clinical Investigations) via encrypted email, only a DoD email address will be used (such as mil@mail.mil or civ@mail.mil). Study information will never be sent to a civilian email or any other email address. Also, only de-identified data will be sent via email and this will be protected by the U.S. Army and WBAMC firewalls, which in theory will prevent any breech of this information. Encryption will also be used to add another level of security to email correspondence.

Information for this study will never be posted or stored on any social media website, blog or online database (such as Google Drive, Google Documents, Dropbox, etc.). Any publication of this data or

presentations regarding study findings will proceed only after required approval by the WBAMC authorities governing such actions.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Ideally, this study will determine that lower doses of IM ketorolac, given in the emergency department for moderate pain, can achieve equal analgesia compared to high dose of IM ketorolac. We anticipate that there will be a lower rate of adverse outcomes by utilizing lower doses of ketorolac. These findings result in several benefits to the DoD service member and beneficiary. First, by showing a lower rate of adverse outcomes, treating with the lower dose may help improve readiness by decreasing lost man power time. Secondly, reducing the amount of adverse effects while maintaining the same level of therapy, patient satisfaction may improve, as well. Additionally, the outcomes of this study may be used to build a larger, multicenter study to create data which could be generalized to a larger, more complex group of individuals.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

During the recruitment phase, the subjects' name, MRN, and Subject Study Number will be annotated on the master key. The master key will be a paper document which will be maintained by the investigator for the duration of the study. It will be secured in a padlocked locker within the WBAMC ED for the duration of the study.

The recruitment phase will be initiated in the waiting room by requesting them to step off to a more private, secluded portion, where they will be given the verbal synopsis (enclosed) by the PI or AI. Within this secluded portion, an enclosed room, within the Emergency Department the potential subject will complete the pre-screening and consent processes.

During the consent process, the study subjects will fill-out, sign, and date Informed Consent Form and HIPAA Authorization Form. These forms, with PII, will be maintained and secured in the same manner as the master key. The Subject Study Packets, containing the Ketorolac Research Form and VAS forms, will contain PHI but no PII as these forms will be annotated with only the Subject Study Number and will be de-identified (no PII will be on these documents). However, these forms will be secured in the same manner as the other forms.

Upon completion of the data collection phase, all forms will be transferred securely to WBAMC room 10015 and secured in a locked cabinet or locker, behind a locked door (secured with a cypher lock) for a minimum of two years following the completion of this study, in accordance with IRB and WBAMC policies.

The single electronic document will be the Excel worksheet used to compile all study subject data. The document will be located on the PIs government issued laptop. This worksheet will be password protected and saved to the hard drive of the PIs laptop. The hard drive on the computer can only be accessed by the person who saved it and network system administrators. All measures have been created to protect the information of the study though there will not be any PHI or PII on the document. This document will be destroyed upon completion of the dissertation defense.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

Due to the study design, incidental or unexpected findings are highly unlikely. Ketorolac is an NSAID which has held FDA approval since May 16, 1997[25]. The study is designed to compare two doses of ketorolac which are very commonly used to treat pain in EDs and in other areas of medicine nationwide.

However, any incidental or unexpected findings will be discussed with the patient and the attending provider. If permission is granted from the attending provider and patient in written form (through the use of a medical disclosure form) and shared with the appropriate WBAMC authorities and the DCI. However, again, these findings are highly unlikely for this study and with the use of such a well understood medication such as ketorolac.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- ○ DSMP
- ○ DSMB
- ○ Both
- ◉ Not Applicable

16.0 Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

All unanticipated problems involving risk to subjects or others, unexpected serious adverse events, and all subject deaths related or possibly related to the study will be reported promptly providing initial notification of the event as quickly as possible after the research team's knowledge of the event, but within five (5) business days of identification by phone (210-916-0606/2598), by e-mail (usarmy.jbsa.medcom-bamc.mbx.bamc-irb@mail.mil), by facsimile (210-916-1650) or via letter addressed to IRB Administrator, Regional Health Command-Central Office of the Institutional Review Board, Brooke Army Medical Center, Attn: MCHE-ZQ, Department of Quality and Safety, 3551 Roger Brooke Drive, Fort Sam Houston, TX 78234-6315. A complete written report will follow the initial notification within 10 working days.

Reportable events may include any serious adverse event directly related to the administration of intramuscular ketorolac during the conduct of this study; such as hospitalization, GI bleed, anaphylaxis, infection at the injection site, death, or other unexpected adverse event which requires additional treatment.

Any expected adverse events (i.e. risks outlined in section 14.1 of this protocol) will be documented in the adverse events log and submitted to the IRB at the time of continuing review.

The study team will consult with the William Beaumonth Human Resarch Protections Office for assistance in submitting any reportable events.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

☑ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

☑ Are drug(s) in this research being used in accordance to the approved labeling?
☐ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** KETOROLAC **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	KETOROLAC
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Roche
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes

Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	N/A
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	15mg-60mg
Frequency:	Once
Route of administration:	IM
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	N/A
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	Emergency Department nursing staff caring for the subjects will prepare drug for administration.
Indication(s) under Investigation:	Acute Musculoskeletal Pain
Where will the drug be stored	Within the Emergency Department medication omnicell.
Drug Storage Restrictions (including temperature, etc.):	The medication is stored in accordance with William Beaumont Pharmacy policies.
Administration Instructions:	The medication should be administered slowly and deeply into the muscle, in accordance with product labeling.
Possible Untoward Effects, Their Symptoms & Treatment:	Nausea, vomiting, abdominal pain, drowsiness, and lethargy, Patients should be managed by symptomatic and supportive care following overdose
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	N/A
	Ketorolac Tromethamine is contraindicated in patients with previously demonstrated hypersensitivity to ketorolac. Warnings include The total combined duration of use of oral ketorolac tromethamine and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine is not indicated for use in pediatric patients. The most serious risks associated with ketorolac tromethamine are: Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation Ketorolac tromethamine is contraindicated in patients with previously documented peptic ulcers and/or GI bleeding. Ketorolac tromethamine can cause serious gastrointestinal (GI) adverse events including bleeding, ulceration and perforation, of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with ketorolac tromethamine.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. The incidence and severity of gastrointestinal complications increases with increasing dose of, and duration of treatment with, ketorolac tromethamine. Do not use ketorolac tromethamine for more than five days.

However, even short-term therapy is not without risk. In addition to past history of ulcer disease, other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids, or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of ketorolac tromethamine until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn’s disease) as their condition may be exacerbated.

Hemorrhage

Because prostaglandins play an important role in hemostasis and NSAIDs affect platelet aggregation as well, use of ketorolac tromethamine in patients who have coagulation disorders should be undertaken very cautiously, and those patients should be carefully monitored. Patients on therapeutic doses of anticoagulants (e.g., heparin or dicumarol derivatives) have an increased risk of bleeding complications if given ketorolac tromethamine concurrently; therefore, physicians should administer such concomitant therapy only extremely cautiously. The concurrent use of ketorolac tromethamine and therapy that affects hemostasis, including prophylactic low-dose heparin (2500 to 5000 units q12h), warfarin and dextrans have not been studied extensively, but may also be associated with an increased risk of bleeding. Until data from such studies are available, physicians should carefully weigh the benefits against the risks and use such concomitant therapy in these patients only extremely cautiously.

Patients receiving therapy that affects hemostasis should be monitored closely.

In postmarketing experience, postoperative hematomas and other signs of wound bleeding have been reported in association with the peri-operative use of IV or IM dosing of ketorolac tromethamine. Therefore, peri-operative use of ketorolac tromethamine should be avoided and postoperative use be undertaken with caution when hemostasis is critical (see PRECAUTIONS).

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of

Contraindications and Interactions, If Known:	NSAID therapy is usually followed by recovery to the pretreatment state. Ketorolac tromethamine and its metabolites are eliminated primarily by the kidneys, which, in patients with reduced creatinine clearance, will result in diminished clearance of the drug (see CLINICAL PHARMACOLOGY). Therefore, ketorolac tromethamine should be used with caution in patients with impaired renal function (see DOSAGE AND ADMINISTRATION) and such patients should be followed closely. With the use of ketorolac tromethamine, there have been reports of acute renal failure, interstitial nephritis and nephrotic syndrome. Impaired Renal Function Ketorolac tromethamine is contraindicated in patients with serum creatinine concentrations indicating advanced renal impairment (see CONTRAINDICATIONS). Ketorolac tromethamine should be used with caution in patients with impaired renal function or a history of kidney disease because it is a potent inhibitor of prostaglandin synthesis. Because patients with underlying renal insufficiency are at increased risk of developing acute renal decompensation or failure, the risks and benefits should be assessed prior to giving ketorolac tromethamine to these patients. Interactions include Ketorolac is highly bound to human plasma protein (mean 99.2%). There is no evidence in animal or human studies that ketorolac tromethamine induces or inhibits hepatic enzymes capable of metabolizing itself or other drugs. Warfarin, Digoxin, Salicylate, and Heparin: The in vitro binding of warfarin to plasma proteins is only slightly reduced by ketorolac tromethamine (99.5% control vs 99.3%) when ketorolac plasma concentrations reach 5 to 10 mcg/mL. Ketorolac does not alter digoxin protein binding. In vitro studies indicate that, at therapeutic concentrations of salicylate (300 mcg/mL), the binding of ketorolac was reduced from approximately 99.2% to 97.5%, representing a potential twofold increase in unbound ketorolac plasma levels. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, piroxicam, acetaminophen, phenytoin and tolbutamide did not alter ketorolac tromethamine protein binding. In a study involving 12 adult volunteers, oral ketorolac tromethamine was coadministered with a single dose of 25 mg warfarin, causing no significant changes in pharmacokinetics or pharmacodynamics of warfarin. In another study, ketorolac tromethamine dosed IV or IM was given with two doses of 5000 U of heparin to 11 healthy volunteers, resulting in a mean template bleeding time of 6.4 minutes (3.2 to 11.4 min) compared to a mean of 6 minutes (3.4 to 7.5 min) for heparin alone and 5.1 minutes (3.5 to 8.5 min) for placebo. Although these results do not indicate a significant interaction between ketorolac tromethamine and warfarin or heparin, the administration of ketorolac tromethamine to patients taking anticoagulants should be done extremely cautiously, and patients should be closely monitored (see WARNINGS and PRECAUTIONS: Hematologic Effect). The effects of warfarin and NSAIDs, in general, on GI bleeding are synergistic, such that the users of both drugs together have a risk of serious GI bleeding higher than the users of either drug alone. Aspirin: When ketorolac tromethamine is administered with aspirin, its protein binding is reduced, although the clearance of free ketorolac tromethamine is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of ketorolac tromethamine and aspirin is not generally recommended because of the potential of increased adverse effects. Diuretics: Clinical studies, as well as postmarketing observations,

have shown that ketorolac tromethamine can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS: Renal Effects), as well as to assure diuretic efficacy.

Probenecid: Concomitant administration of oral ketorolac tromethamine and probenecid resulted in decreased clearance and volume of distribution of ketorolac and significant increases in ketorolac plasma levels (total AUC increased approximately threefold from 5.4 to 17.8 mcg/h/mL) and terminal half-life increased approximately twofold from 6.6 to 15.1 hours. Therefore, concomitant use of ketorolac tromethamine and probenecid is contraindicated.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

ACE Inhibitors/Angiotensin II Receptor Antagonists: Concomitant use of ACE inhibitors and/or angiotensin II receptor antagonists may increase the risk of renal impairment, particularly in volume-depleted patients.

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors and/or angiotensin II receptor antagonists. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors and/or angiotensin II receptor antagonists.

Antiepileptic Drugs: Sporadic cases of seizures have been reported during concomitant use of ketorolac tromethamine and antiepileptic drugs (phenytoin, carbamazepine).

Psychoactive Drugs: Hallucinations have been reported when ketorolac tromethamine was used in patients taking psychoactive drugs (fluoxetine, thiothixene, alprazolam).

Pentoxifylline: When ketorolac tromethamine is administered concurrently with pentoxifylline, there is an increased tendency to bleeding.

Nondepolarizing Muscle Relaxants: In postmarketing experience there have been reports of a possible interaction between ketorolac tromethamine IV/IM and nondepolarizing muscle relaxants that resulted in apnea. The concurrent use of ketorolac tromethamine with muscle relaxants has not been formally studied.

Selective Serotonin Reuptake Inhibitors (SSRIs): There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be used when NSAIDs are administered concomitantly with SSRIs.

Carcinogenesis, Mutagenesis and Impairment of Fertility

An 18-month study in mice with oral doses of ketorolac tromethamine at 2 mg/kg/day (0.9 times the human systemic exposure at the recommended IM or IV dose of 30 mg qid, based on area-under-the-plasma-concentration curve [AUC]), and a 24-month study in rats at 5 mg/kg/day (0.5 times the human AUC) showed no evidence of tumorigenicity.

Ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the in vivo mouse micronucleus assay. At 1590 mcg/mL and at higher

	concentrations, ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells. Impairment of fertility did not occur in male or female rats at oral doses of 9 mg/kg (0.9 times the human AUC) and 16 mg/kg (1.6 times the human AUC) of ketorolac tromethamine, respectively. tromethamine. Ketorolac tromethamine is contraindicated in patients with active peptic ulcer disease, in patients with recent gastrointestinal bleeding or perforation and in patients with a history of peptic ulcer disease or gastrointestinal bleeding. Ketorolac tromethamine should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS – Anaphylactoid Reactions, and PRECAUTIONS – Preexisting Asthma). Ketorolac tromethamine is contraindicated as prophylactic analgesic before any major surgery. Ketorolac tromethamine is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS). Ketorolac tromethamine is contraindicated in patients with advanced renal impairment or in patients at risk for renal failure due to volume depletion (see WARNINGS for correction of volume depletion). Ketorolac tromethamine is contraindicated in labor and delivery because, through its prostaglandin synthesis inhibitory effect, it may adversely affect fetal circulation and inhibit uterine musculature, thus increasing the risk of uterine hemorrhage. The use of ketorolac tromethamine is contraindicated in nursing mothers because of the potential adverse effects of prostaglandin-inhibiting drugs on neonates. Ketorolac tromethamine inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see WARNINGS and PRECAUTIONS). Ketorolac tromethamine is contraindicated in patients currently receiving asprin or NSAIDs because of the cumulative risks of inducing serious NSAID-related adverse events. The concomitant use of ketorolac tromethamine and probenecid is contraindicated. The concomitant use of ketorolac tromethamine and pentoxifylline is contraindicated. Ketorolac tromethamine injection is contraindicated for neuraxial (epidural or intrathecal) administration due to its alcohol content.
Investigators Authorized to Prescribe:	CPT Nathaniel J. Turner and MAJ Joseph R. Bongiorno.

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

N/A

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ○ Registration is not required
- ◉ Registration pending
- ○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ○ Registration is not required
- ◉ Registration pending
- ○ Registration complete

20.0 References and Glossary

20.1 References:

1. Motov, S. *et al.* Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial. *Ann.Emerg. Med.* 70, 177–184 (2017).

2. Catapano, M. S. The analgesic efficacy of ketorolac for acute pain. *J. Emerg. Med.* 14, 67–75 (1996).

3. Jones, S. F. & O'Donnell, A. M. Clinical pharmacology: traditional NSAIDs and selective COX-2 inhibitors. *Clinical Pain Management Second Edition: Acute Pain* 1, 168 (2008).

4. García Rodríguez, L. A., Cattaruzzi, C., Troncon, M. G. & Agostinis, L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch. Intern. Med.* 158, 33–39 (1998).

5. Singer, A. J., Mynster, C. J. & McMahon, B. J. The effect of IM ketorolac tromethamine on bleeding time: a prospective, interventional, controlled study. *Am. J. Emerg. Med.* 21, 441–443 (2003).

6. Greer, I. A. Effects of ketorolac tromethamine on hemostasis. *Pharmacotherapy* 10, 71S–76S (1990).

7. Dordoni, P. L. *et al.* Effect of ketorolac, ketoprofen, and nefopam on platelet function. A*naesthesia* 49, 1046–1049 (1994).

8. Gallagher, J. E., Blauth, J. & Fornadley, J. A. Perioperative ketorolac tromethamine and postoperative hemorrhage in cases of tonsillectomy and adenoidectomy. *Laryngoscope* 105, 606–609 (1995).

9. Cawthorn, T. R., Phelan, R., Davidson, J. S. & Turner, K. E. Retrospective analysis of perioperative ketorolac and postoperative bleeding in reduction mammoplasty. *Can. J. Anaesth.* 59, 466–472 (2012).

10. Should Dose Capping Parenteral Ketorolac Be the Standard? Available at: https://www.pharmacytimes.com/contributor/alexander-kantorovich-pharmd-cps/2017/06/shoulddose-capping-parenteral-ketorolac-be-the-standard-/. (Accessed: 24th June 2018)

11. Baker, H. Illustrated Medical Dictionary. (2004).

12. Staquet, M. J. A Double-Blind Study with Placebo Control of Intramuscular Ketorolac Tromethamine in the Treatment of Cancer Pain. *J. Clin. Pharmacol.* 29, 1031–1036 (1989).

13. Reuben, S. S., Connelly, N. R., Lurie, S., Klatt, M. & Gibson, C. S. Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine in patients after spinal

fusion surgery. *Anesth. Analg.* 87, 98–102 (1998).

14. Minotti, V. *et al.* A double-blind study comparing two single-dose regimens of ketorolac with diclofenac in pain due to cancer. *Pharmacotherapy* 18, 504–508 (1998).

15. Peirce, R. J., Fragen, R. J. & Pemberton, D. M. Intravenous ketorolac tromethamine versus morphine sulfate in the treatment of immediate postoperative pain. *Pharmacotherapy* 10, 111S–115S (1990).

16. Brown, C. R., Moodie, J. E., Wild, V. M. & Bynum, L. J. Comparison of intravenous ketorolac tromethamine and morphine sulfate in the treatment of postoperative pain. *Pharmacotherapy* 10, 116S–121S (1990).

17. Soleyman-Zomalan, E. *et al.* Patterns of Ketorolac dosing by emergency physicians. *World J Emerg Med* 8, 43–46 (2017).

18. Tintinalli, J. E., Stephan Stapczynski, J., John Ma, O., Cline, D. M. & Meckler, G. D. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th edition*. (McGraw Hill Professional, 2016).

19. Food and Drug Administration. Toradol® oral (ketorolac tromethamine tablets). Roche Laboratories Inc. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019645s019lbl.pdf. (Accessed: 24th June 2018).

20. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. December 2001;38:633-638.

21. Milley, Mark. GEN Mark Milley to the U.S. Army. 2015. Retrieved on 13 August, 2019. https://www.army.mil/article/154803/39th_chief_of_staff_initial_message_to_the_arm

22. Gupta, S. (2011). Non-inferiority clinical trials: Practice issues and current regulatory perspective. Indian Journal of Pharmacology, 43(4), 371-374.

23. Emergency Severity Index (ESI): A Triage Tool for Emergency Departments. Content last reviewed May 2018. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov /professionals/systems/hospital/esi/index.html

24. Marion, DW. Ketorolac (systemic): Drug Information. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2019.

25. Quidel (2019). *QuickVue HCG Urine.*

26. U.S. Food and Drug Administration. (2016, January). Retrieved from **https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/74754_Ketorolac.cfm**

20.2 Abbreviations and Acronyms:

Cyclooxygenase-1 (COX-1)
Cyclooxygenase-2 (COX-2)
Department of Defense (DoD)
Department of Veterans Affairs (VA)
Electronic Health Record (EHR)
Emergency Department (ED)
Emergency Severity Index (ESI)
Food and Drug Administration (FDA)
Health Insurance Portability and Accountability Act (HIPAA)
Human-Chorionic Gonadotropin (HCG)
Intramuscular (IM)
Intravenous (IV)
Medical Record Number (MRN)
Milligram (mg)
Milliliter (mL)
Millimeter (mm)
Millimeters of Mercury (mmHg)
Minimum Clinical Significant Difference (MCSD)
Nonsteroidal anti-inflammatory drug (NSAID)
Primary Investigator (PI)
Protected Health Information (PHI)
Personally Identifiable Information (PII)
Visual Analog Scale (VAS)

William Beaumont Army Medical Center (WBAMC)	