Major Extremity Trauma Research Consortium (METRC):

Improving Pain Management and Long Term Outcomes Following High Energy Orthopedic Trauma (Pain Study)

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This template is adapted from the ICH guidance document E6 (Good Clinical Practices), Section 6.

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

The Lead Principal Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal Investigator: ____________________________________________

Print/Type

Signed: __________________________________ Date: ________________

Name/Title
## CONTENTS

Signature Page................................................................................................................................. ii

PROTOCOL SUMMARY ..................................................................................................................... 9

1. KEY ROLES ................................................................................................................................. 17

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE ................................. 18
   2.1 Background Information ........................................................................................................ 18
   2.2 Rationale ................................................................................................................................. 21
   2.3 Potential Risks and Benefits ................................................................................................. 22

3. STUDY OBJECTIVES ..................................................................................................................... 24
   3.1 Primary Objective .................................................................................................................... 24
   3.2 Secondary Objectives ............................................................................................................. 24

4. STUDY DESIGN ............................................................................................................................. 25
   4.1 Description of the Study Design ............................................................................................. 25
   4.2 Study Endpoints ....................................................................................................................... 27

5. STUDY POPULATION .................................................................................................................... 27
   5.1 Description of the Study Population ....................................................................................... 27
   5.2 Strategies for Recruitment ........................................................................................................ 29

6. STUDY TREATMENTS .................................................................................................................... 30
   6.1 Description of the Study Treatment Arms ............................................................................... 30
   6.2 Study Agent Administration .................................................................................................... 35
   6.3 Concomitant Medications and Procedures .............................................................................. 35
   6.4 Assessment of Participant Adherence with Study Agent(s)/Intervention(s) ......................... 35
   6.5 Precautionary and Prohibited Medications and Procedures ................................................. 35
7. STUDY PROCEDURES/EVALUATIONS ................................................................. 35

7.1 Clinical Evaluation.......................................................................................... 36

7.2 Laboratory Evaluations .................................................................................. 38

7.3 Assessment of Participant Compliance with Study ......................................... 38

8. STUDY SCHEDULE .......................................................................................... 39

8.1 Screening ........................................................................................................... 39

8.2 Enrollment/Baseline ......................................................................................... 39

8.3 Randomization .................................................................................................. 40

8.4 Follow-up ........................................................................................................... 40

8.5 Final Study Visit ............................................................................................... 41

8.6 Early Termination Visit N/A ............................................................................. 41

8.7 Pregnancy Visit ................................................................................................ 41

8.8 Unscheduled Visits .......................................................................................... 41

9. ASSESSMENT OF SAFETY ............................................................................... 42

9.1 Definitions ........................................................................................................ 42

9.2 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters .......................................................... 43

9.3 Adverse Event Reporting Procedures .............................................................. 44

9.4 Reporting Pregnancy ......................................................................................... 46

9.5 Type and Duration of the Follow-up of Participants After Adverse Events ........ 46

9.6 Modifications of Study Agent(s)/Intervention(s) for a Participant .................... 46

9.7 Halting Rules for the Protocol ........................................................................ 47

9.8 Stopping Rules for an Individual Participant/Cohort ........................................ 47

9.9 Premature Withdrawal of a Participant ........................................................... 47

9.10 Replacement of a Participant Who Discontinues Study Treatment N/A .......... 47

10. CLINICAL MONITORING STRUCTURE ..................................................... 47
11. STATISTICAL CONSIDERATIONS ......................................................... 49
11.1 Overview and Study Objectives ......................................................... 49
11.2 Sample Size Considerations ............................................................... 49
11.3 Randomization .................................................................................. 51
11.4 Missing Data ..................................................................................... 51
11.5 Planned Interim Analysis ................................................................... 51
11.6 Analysis Plan .................................................................................... 52

12. QUALITY CONTROL AND QUALITY ASSURANCE ................................. 53

13. ETHICS/PROTECTION OF HUMAN SUBJECTS ........................................ 53
13.1 IRB/Ethics Committee ....................................................................... 53
13.2 Informed Consent Process .................................................................. 54

All recruitment materials will be provided in both English and Spanish. ............ 54

13.2.2 Assessing Capacity to Consent and Consenting a Proxy Respondent .......... 54

13.3 Exclusion of Women, Minorities, and Children (Special Populations) .......... 55

13.4 Participant Confidentiality .................................................................. 55

13.5 Study Discontinuation ....................................................................... 55

14. DATA HANDLING AND RECORD KEEPING ............................................. 55
14.1 Data Management Responsibilities ....................................................... 55
14.2 Data Capture Methods ....................................................................... 56
14.3 Types of Data .................................................................................... 57

14.4 Source Documents and Access to Source Data/Documents .......................... 57

14.5 Timing/Reports ................................................................................ 57

14.6 Study Records Retention ................................................................... 57
14.7 Protocol Deviations ........................................................................................................... 57

15. PUBLICATIONS POLICY .................................................................................................. 57

16. SCIENTIFIC REFERENCES ............................................................................................... 57

17. APPENDICES ................................................................................................................... 63

   APPENDIX A: STUDY CONTACT ROSTER ........................................................................ 63

   APPENDIX B: PROTOCOL COMMITTEE .......................................................................... 64

   APPENDIX C: DATA COLLECTION SCHEDULE ............................................................... 65

   APPENDIX D: ADVERSE EVENT GRADING TABLE* .................................................... 68

   APPENDIX E: Common and Infrequent Adverse Events for Study Drugs ...................... 78

   APPENDIX F: CONSENT TEMPLATE ................................................................................. 81

   APPENDIX G: CONSENT TEMPLATE – PILOT STUDY ..................................................... 88

   APPENDIX H: EVALUATION TO GIVE CONSENT ......................................................... 94

   APPENDIX I: STUDY INSERT ............................................................................................ 95

   APPENDIX J: PATIENT DAILY LOG ............................................................................... 102
List of General Abbreviations/Terminology

AE  Adverse Event/Adverse Experience
CFR  Code of Federal Regulations
CIB  Clinical Investigator’s Brochure
CONSORT  Consolidated Standards of Reporting Trials
CRF  Case Report Form
DSMB  Data and Safety Monitoring Board
DSMC  Data and Safety Monitoring Committee
FDA  Food and Drug Administration
FWA  Federal-Wide Assurance
GCP  Good Clinical Practice
HIPAA  Health Insurance Portability and Accountability Act
IB  Investigator’s Brochure
ICF  Informed Consent Form
ICH  International Conference on Harmonization
IDE  Investigational Device Exemption
IND  Investigational New Drug
IRB  Institutional Review Board
ISM  Independent Safety Monitor
MedDRA ©  Medical Dictionary for Regulatory Activities
MOP  Manual of Procedures
NDA  New Drug Application
OHRP  Office for Human Research Protections
OHSR  Office for Human Subjects Research
PHI  Protected Health Information
PI  Principal Investigator
PK  Pharmacokinetics
QA  Quality Assurance
QC  Quality Control
SAE  Serious Adverse Event/Serious Adverse Experience
SMC  Safety Monitoring Committee
SOP  Standard Operating Procedure
WHO  World Health Organization
### List of METRC Abbreviations/Terminology

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDMRP</td>
<td>Congressionally Directed Medical Research Program.</td>
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<tr>
<td>DOD</td>
<td>Department of Defense</td>
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<tr>
<td>DOD HRPO</td>
<td>DOD Human Research Subject Protection Office.</td>
</tr>
<tr>
<td>Master Consent Form</td>
<td>Template consent form designed for study by the MCC</td>
</tr>
<tr>
<td>Master IRB application</td>
<td>Template IRB application designed for study by the MCC</td>
</tr>
<tr>
<td>MCC</td>
<td>METRC Coordinating Center</td>
</tr>
<tr>
<td>MCC Study Manager</td>
<td>Principal site contact for Research Coordinators at sites</td>
</tr>
<tr>
<td>MTF Core Clinical Sites</td>
<td>Military Treatment Facilities Core Clinical</td>
</tr>
<tr>
<td>OETRP</td>
<td>Orthopaedic Extremity Trauma Research Program</td>
</tr>
<tr>
<td>SCC</td>
<td>Satellite Clinical Sites</td>
</tr>
<tr>
<td>AI</td>
<td>Site Associate Investigators.</td>
</tr>
<tr>
<td>RC</td>
<td>Site Research Coordinator</td>
</tr>
<tr>
<td>RS</td>
<td>Site Research Staff</td>
</tr>
<tr>
<td>Study Number</td>
<td>Protocol identification number</td>
</tr>
<tr>
<td>Study Principal Investigator</td>
<td>Lead Investigator on a protocol</td>
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<tr>
<td>Study Protocol Committee</td>
<td>Protocol development</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedures</td>
</tr>
<tr>
<td>REDCap</td>
<td>Research Electronic Data Capture System</td>
</tr>
<tr>
<td>USAMRMC</td>
<td>United States Army Medical Research and Material Command</td>
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</tbody>
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PROTOCOL SUMMARY

Title: Improving Pain Management and Long Term Outcomes Following High Energy Orthopedic Trauma

Financial Sponsor: DoD CDMRP / National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Type of study: The proposed study is a three arm, double blinded, randomized, placebo controlled multicenter Phase III clinical trial.

Objective: The objective of this study is to definitively resolve questions regarding the use of multimodal pharmacologic pain management for orthopedic trauma patients in the context of a multicenter, randomized clinical trial. We will test whether adjunctive analgesic therapy during the pre and peri-operative period, in addition to standard of care pain management, can improve overall pain control and pain related outcomes without increasing analgesic related side effects.

As a significant proportion of this population develops chronic post traumatic osteoarthritis (PTOA), a sub-objective of this study is to examine the etiology and incidence of chronic pain and PTOA in this population.

Study Groups: Patients will be randomized into three treatment groups. The intervention will begin within 48 hours of admission and continue for no longer than two weeks or up to 48 hours after definitive fixation.

- **Group 1**: standard pain management, plus up to two weeks of oral placebo, plus intravenous and oral placebo for up to 48 hours at each surgical procedure.

- **Group 2**: standard pain management, plus up to two weeks of oral non-steroidal anti-inflammatory drugs (NSAIDs) (meloxicam), plus intravenous NSAIDs (ketorolac) and oral placebo for up to 48 hours at each surgical procedure.

- **Group 3**: standard pain management, plus up to two weeks of oral pregabalin, plus intravenous placebo and oral pregabalin for up to 48 hours at each surgical procedure.

Specific Aim 1: Evaluate the effect of standard pain management (Group 1) vs. standard pain management plus pre and peri-operative NSAIDs (Group 2 – meloxicam + ketorolac) in the treatment of severe limb fractures.

*Hypothesis 1a*: When compared to patients who received standard of care pain management, patients treated with NSAIDs will: (1) have reduced post operative opioid utilization; (2) report reduced levels of persistent pain; and (3) have noninferior rates of surgery for nonunion.
Hypothesis 1b: When compared to patients who received standard of care pain management, patients treated with NSAIDs will benefit from (1) improved post operative pain control; (2) improved pre operative pain control; (3) reduced lengths of stay; (4) reduced pain interference; (5) improved functional outcomes; (6) lower levels of depression and post-traumatic stress disorder (PTSD); (7) improved overall health status; and (8) have noninferior rates of analgesic treatment related side effects.

Specific Aim 2: Evaluate the effect of standard pain management (Group 1) vs. standard pain management plus pre and peri-operative pregabalin (Group 3) in the treatment of severe limb fractures.

Hypothesis 2a: When compared to patients who received standard of care pain management, patients treated with pregabalin will: (1) have reduced post operative opioid utilization; (2) report reduced levels of persistent pain; and (3) have noninferior rates of surgery for nonunion.

Hypothesis 2b: When compared to patients who received standard of care pain management, patients treated with pregabalin will benefit from (1) improved post operative pain control; (2) improved pre operative pain control; (3) reduced lengths of stay; (4) reduced pain interference; (5) improved functional outcomes; (6) lower levels of depression and post-traumatic stress disorder (PTSD); (7) improved overall health status; and (8) have noninferior rates of analgesic treatment related side effects.

Specific Aim 3: Estimate the incremental cost effectiveness of each adjunctive analgesic therapy relative to standard of care analgesic therapy in the treatment of severe limb fractures. Costs will be estimated from both the health care provider perspective and the societal perspective. The time horizon for cost-effectiveness analysis will be based on the actual period of observation. Incremental cost-effectiveness ratios will be calculated for: (a) study group 2 (NSAIDS – meloxicam + ketorolac) relative to standard of care; and (b) study group 3 (pregabalin) relative to standard of care. For purpose of cost-effectiveness analysis, the effect will be measured as unit change in specific outcome metrics at 12 months (or longer period as available) compared to baseline. The following cost-effectiveness metrics, all relative to standard of care, will be reported:

1. incremental cost per unit change in the Brief Pain Inventory
2. incremental cost per unit change in the Short Muscular Function Assessment (SFMA)
3. incremental cost per unit change in health state preference (“utility”) as derived from the VR-12

PTOA Pilot Study: Additional funding was received from NIH to conduct a pilot, observational study of post-traumatic osteoarthritis (PTOA), leveraging current resources of the Pain study. PTOA is an important outcome in the population to be enrolled in the Pain study. The aims of the PTOA Study are to: (1) measure the incidence of PTOA and chronic pain for up to 24 months following fracture reduction surgery and (2) quantify the extent to which fracture severity and post-reduction contact stress are related to the development of PTOA. Accomplishment of these aims will require (1) for all patients with ankle fractures in the Pain study: complete a PTOA
survey at 12 months and at any subsequent visits that are conducted as part of standard of care and provide access to all standard of care imaging studies completed during the study period and (2) for a subset of 60 pilon fracture patients enrolled in the Pain study for whom post-operative CT scans are not standard of care, obtain additional consent for completion of a study-funded post-operative CT scan and 24 month radiographic study.

Study design: Three-arm, double blinded, randomized, placebo controlled Phase III clinical trial.

Study Follow-Up: All study participants will be followed for 12 months to assess pain, functional outcome, medical costs and adverse events. If standard of care at their institution, participants will also be followed up to 24 months to study the development of PTOA. A subset of pilon fracture patients (n=60), for whom long term follow-up is not standard of care, will be followed up to 24 months to assess their development of PTOA.

Study duration: 3.75 years (18 month accrual, 24 month final follow-up, 3 month analysis and writing).

Sample size: 495 (165 per (3) arms); 60 pilon fracture patients will be consented for additional data collection related to the PTOA pilot study (specific aim 4).

Number of study sites: 20-25 METRC sites (10-15 Civilian Core Clinical and Military Treatment Facility Core Clinical Sites and approximately 10 Satellite Clinical sites) will have the opportunity to participate in this study.

Study population: Inclusion and exclusion criteria were developed to select a study population of patients with orthopaedic trauma known to experience moderate to high rates of chronic pain and nonunion: patients with fractures to the ankle and midfoot, the tibia, the humerus, and the femur. Since military combat injuries are typically thought of as open, we will include all Grade I/II and some Grade IIIA open fracture types in our study. However, since post surgical pain is not limited to the open fractures, and the concept of perioperative pain management should apply to both open and closed injuries, we will also include closed versions of these high-energy injuries in our study population.

Inclusion criteria

1. Patients with one of the following types of injuries:
   a. Unilateral, Grade I &II open or closed pilon (distal tibial plafond), calcaneus, talus fractures and Lisfranc dislocations requiring operative treatment with fixation; or
   b. Unilateral, open (type I, II, or IIIA) ankle fractures with associated dislocation on presentation (OTA 44B3 or 44C) requiring operative treatment with fixation; or
   c. Unilateral, open or closed distal and proximal humerus (OTA 11A-C and OTA 13 A-C); or
   d. Open femoral shaft fracture (OTA 32 A-C; Gustilo Type I-IIIC) or open or closed supracondylar femur fractures (OTA 33 A-C); or
e. Open or closed tibial plateau or shaft fractures (OTA 42 A-C or 43 A-C)
f. Any combination of the above injuries which are surgically treated as a whole

2. Patients who present to the admitting hospital acutely or clinic following an initial assessment in the Emergency Department, for care up to 10 days following initial injury.
3. Patients 18-80 years old inclusive.
4. Patients who are English or Spanish competent.
5. Treating physicians agree that none of the study drugs are indicated for standard of care treatment for this patient.
6. Patients able to be followed at the METRC facility for at least 12 months following injury.

Exclusion criteria

1. Patients unable to provide informed consent.
2. Patients with chronic pain being presently treated with opioid or gabapentinoid prescription or any other alternative therapy.
3. Patients who are current IVDA
4. Patients with bilateral or ipsilateral injuries requiring surgery
5. Patients with other orthopedic or non-orthopedic injuries requiring operative intervention
6. Patients with severe osteopenia.
7. Patients who are skeletally immature (defined as less than 18 years of age or no radiographic evidence of epiphyseal closure).
8. Patients who are expected to have a post-surgical stay less than 24 hours.
9. Patients with a history of allergy to any drugs in the study.
10. Patients unable to swallow oral medications or without adequately functioning GI tract.
11. Patients with a history of gastrointestinal bleeds or gastric perforation.
12. Patients currently receiving an aspirin or NSAID regimen (exception: low dose (81 mg) aspirin. See section 6.5) Patients with any bleeding disorders.
13. Patients with severe renal failure. Patients with moderate renal failure may participate in the study at a modified dose. See Section 9.6.
15. Patients using angiotensin-converting enzyme (ACE) inhibitors, who may be at increased risk of developing angioedema with pregabalin.
16. Patients likely to have severe problems maintaining follow-up, including patients diagnosed with a severe psychiatric conditions, patients who live too far outside the hospital’s catchment area, patients who are incarcerated and patients who have unstable housing situations.
17. Patients who experienced a loss of consciousness consistent with a clinical diagnosis of a closed head injury, or concern of a cerebrovascular bleed secondary to traumatic brain injury.
18. Patients with a GCS <15
19. Patient speaks neither English nor Spanish.
20. Patients who are pregnant or lactating at time of screening

Study Endpoints
Patients will be followed for a minimum of 12 months following their injury, at which point a final assessment of utilization and patient reported outcomes will be conducted for Specific Aims 1-3 (see Outcome Measures). Final clinical assessments and radiographs obtained as close to 12 months as routine practice allows. At practices where patients are routinely followed for more than 12 months, clinical assessments and radiographs taken per standard of care for up to 24 months will also be included in the study, at which point all study-related activities will be completed. A subset of 60 pilon fracture patients for whom post-operative CT scans are not routinely conducted per standard of care, identified prospectively, will provide an additional CT up to 3 months following definitive fixation, and will provide a final set of radiographs 24 months following definitive fixation.

**Outcome Measures**

**Primary Outcome Measures:**

All post operative follow up time points assume a 2 week window before and after the scheduled visit.

Opioid Utilization: Morphine equivalent opioid utilization during the 48 hours following definitive fixation or discharge, whichever comes first.

Persistent Pain: Patient reported persistent pain states at standard of care visits 3, 6 and 12 months following injury. Measured using the Brief Pain Inventory (BPI) and an additional battery of questions to assess neuropathic pain (painDETECT).

Surgery for non-union: Defined as non-prophylactic surgery for nonunion performed between six months and a year following initial hospital discharge.

**Secondary Outcome Measures**

Post Surgical Pain Intensity: Pain intensity at 12-hour intervals for up to 48 hours following definitive fixation surgery. Abstracted from medical record and supplemented by participant pain logs. At least one time point will be assessed using the Multidimensional Post Surgical Pain Scale in order to study multiple pain dimensions.

Pre Surgical Pain Intensity: Pain intensity at 12-hour intervals between study enrollment and definitive fixation surgery. Abstracted from medical record and supplemented by participant pain logs.

Length of Index Hospitalization: Defined as the hospitalization during which the definitive fixation occurs. Length of stay for all other study injury related hospitalizations will also be abstracted.

**Adverse Effects and Complications:** Will include nonunion, wound closure complications, bleeding complications (particularly perioperative bleeding due to loss of platelet function and gastrointestinal bleeding), as well as pain treatment related adverse effects. These include
nausea, vomiting, constipation, sedation, pruritis, respiratory depression, somnolence, dizziness, headaches, coordination problems, peripheral edema, blurred vision, gastrointestinal symptoms and irritation, renal impairment, platelet inhibition, angioedema, and post operative delirium. Adverse effects and complications will be assessed by both patient report of symptoms during the period between enrollment and up to 48 hours post definitive fixation, and by clinical survey of symptoms during index hospitalization and at discharge from additional surgical admissions up to definitive fixation.

Functional Outcome: The SMFA (Short Musculoskeletal Function Assessment) is a shorter version of the 101-item Musculoskeletal Function Assessment (MFA) questionnaire. The SMFA is a 46-item questionnaire consisting of the dysfunction index and the bother index. The dysfunction index has 34 items for assessment of patient function, while the bother index consists of 12 items designed to detect how much patients are bothered by functional items. The SMFA has been evaluated for reliability, validity and responsiveness in trauma populations. To be assessed at 6 and 12 months following injury.

The Veterans RAND 12 Item Health Survey (VR-12). The VR-12 is included as a generic health status measure from which a VR-6D can be computed for the purpose of a cost-utility analysis. The VR-12 is a multipurpose self-administered generic measure of health status. It was developed to measure health-related quality of life, estimate disease burden and compare disease-specific benchmarks across populations. The VR-12 items measure eight health domains: general health perceptions; physical functioning; role limitations due to physical and emotional problems; bodily pain; energy-fatigue, social functioning and mental health. The instrument produces a physical health and mental health summary measure. To be assessed at 6 and 12 months following injury.

Depressive Symptoms. The presence of depressive symptoms will be measured using the nine item depression scale of the Patient Health Questionnaire (PHQ-9). The PHQ-9 is a well validated tool for assisting clinicians in diagnosing depression. There are two components of the PHQ-9: (1) assessing symptoms and functional impairment to make a tentative depression diagnosis, and (2) deriving a severity score. The PHQ-9 is based directly on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV). To be assessed at 12 months following injury.

Post Traumatic Stress (PTSD). PTSD will be measured using the standard PTSD Checklist (PCL), a 17-item measure that elicits responses for each of the DSM-IV disorders that comprise the diagnostic criteria for PTSD (intrusive, avoidant, and arousal symptoms). The psychometric properties of the PCL have been well established and it is the most widely used measure of PTSD. Both civilian and military versions are available. The military version will be used for all those patients on active duty at the time of their injury. To be assessed at 12 months following injury.

Medical Costs: Costs for the index hospitalization and subsequent hospitalizations (within one year of injury) will be derived using hospital bills, outpatient bills and professional fees. Hospital costs will be calculated from charges at the revenue center/cost department line level using cost-to-charge ratios (CCRs) computed from the hospital-specific Medicare Cost Reports.
Billing data will be supplemented or imputed by identifying medical resource utilization as documented in study case report forms, categorizing resources using standard medical billing codes, and assigning costs based on Medicare fee schedules. Of particular interest will be resource utilization and costs associated with the index hospital admission, surgical procedures for bone grafting and nonunion, subsequent admissions for complications, and post-operative follow-up care.

CT scans: For each patient, standard of care CT scans will be obtained, which will be used to measure fracture severity. In severe fractures, this image will be obtained after application of a temporary joint spanning external fixator. Thus, the fracture severity analysis will be based on fractured distal tibias with limb alignment provisionally controlled. After definitive fracture reconstruction, a second CT scan will be obtained up to 3 months following definitive fixation, for assessment of chronic contact stress challenge. The second CT scan will be obtained for all patients for whom it is standard of care. Among patients for whom the post-operative CT scan is not standard of care, the study will pay for scans in a subset of 60 of the pilon subgroup.

Radiographs: Radiographs of the patient’s injured limb will be obtained at presentation and after each surgical intervention according to standard of care practice. These radiographs will be used for clinical care, to classify the fractures, and at follow-up to assess outcome. Final clinical assessments and radiographs will be obtained as close to 12 months post injury as routine practice allows. At practices where patients are routinely followed for more than 12 months, clinical assessments and radiographs will be conducted at each visit up until 24 months, at which point all study-related activities will be completed. A subset of 60 patients, identified prospectively, will provide an additional CT up to 3 months following definitive fixation, and will provide a final set of radiographs 24 months following definitive fixation. Radiographs obtained beyond 6 months after injury will be taken in the weight bearing position.

PTOA assessment: Among patients in the Pain study, data relevant to the development of PTOA will be collected observationally. All radiographic images, including CT scans and x-rays, taken per standard of care in the first year will be obtained. Additionally, for those patients routinely receiving follow-up beyond 12 months, weight bearing radiographs of the ankle taken at between one and two years after injury will be used to assess and characterize the development of PTOA. In the subset of 60 pilon fracture patients actively recruited into the PTOA pilot study, CT scans taken up to 3 months following definitive fixation, all radiographic images taken per standard of care, in addition to a final set of weight bearing radiographs of the ankle taken at 24 months will be used to assess and characterize the development of PTOA. The presence of PTOA will be determined using the Kellgren and Lawrence (KL) scale. All assessments will be performed by three observers at a single setting (University of Iowa). Ratings will be performed separately to assess agreement, and discrepancies will be resolved by consensus.

Previous literature suggests that although 24 months is too soon to identify end stage manifestations of PTOA, at least 50% of all cases that will eventually develop this condition can be radiographically identified within this time frame. Based on this evidence, 24 month radiographs should allow identification of cases with severe PTOA that commonly follow this injury and will be an adequate follow up interval to meet the goals of this pilot study.
Clinical outcome assessment: A validated ankle score, the Ankle Osteoarthritis Scale (AOS), will be obtained for all patients. It is an 18-item visual analog scale which provides an overall assessment of ankle status as well as specific assessments of pain and disability. To be assessed at 12 months for all patients and up to 24 months for patients in the PTOA pilot study and those observational patients for whom follow-up beyond 12 months is standard of care.

Statistical analysis: Analyses will vary by specific aim. Statistical analyses for the Pain study will follow the intent-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized. For both binary and continuous outcomes, regression modeling may be employed if concerns about confounding arise due to imbalances between treatment groups. Random effects regression modeling may also be used if concerns emerge about the clustering of outcomes within surgeons or centers.

Randomization: Randomization into the Pain study treatment arms will occur in variable permuted blocks, stratified by clinical center. Randomization will be administered centrally by the Data Coordinating Center through the REDCap electronic database.

Safety monitoring: The Medical Monitor is responsible for monitoring serious adverse events (SAEs) as the study progresses to ensure patient safety. The DSMB will review all safety data at its scheduled meetings. The Medical Monitor may convene a meeting of the DSMB to evaluate any SAEs that he/she determines require immediate attention.

Data Safety and Monitoring Board (DSMB): The DSMB is an independent body responsible for evaluating recruitment, safety and outcome data. The DSMB has the authority to stop the study based on its findings.
1. KEY ROLES

Protocol Committee- Responsible for developing a detailed study protocol, provides oversight on study progress and acts to correct deficiencies in the conduct of the study. This committee also drafts the main publications related to the study.

Steering Committee- Steering Committee is the decision making body of the Consortium and makes decisions regarding study design issues, study procedures, allocation of study resources and priorities for meeting competing demands of the Consortium and individual studies. The Steering Committee is composed of Site Investigators from each core METRC clinical center, the Department of Defense Program Officer for METRC, the orthopaedic consultants from the Army, Navy and Air Force, regional representatives of Satellite Clinical Centers, and the Director, Deputy Director, Principal Biostatistician and Principal Economist of the Coordinating Center. The Steering Committee is responsible for approving the protocol.

METRC Coordinating Center- Responsible for maintaining all study documentation, developing and maintaining the master IRB application and consent, circulating any changes to study documents including protocols, case report forms, and IRB materials to each participating center, providing daily oversight and management of study implementation, providing payment to sites for patients enrolled, performing site monitoring, data quality control and analysis of study results.

Core and Satellite Clinical Sites- Responsible for the conduct of clinical studies including patient enrollment, performing study procedures, data collection and conducting study follow-up visits.

Clinical Outcome Adjudication Committee (COAC)- Responsible for developing the timely medical review and adjudication of trial-specific endpoints utilizing trial-specific definitions; engages other reviewers as needed and in accordance with the COAC Policy; and reports adjudication results to the trial-specific Protocol Committee.

Publication Committee- Responsible for reviewing manuscripts prior to journal submission and reviewing presentations prior to presentation; for mediating and settling disputes and conflicts among study investigators over publication or presentation priorities, authorship, and any other issues related to publications or presentations; for preparing and maintaining a list of concepts for publications and preparing and maintaining a list of approved METRC publications, which shows the status of each manuscript from initiation through publication.

DSMB- Independent Data and Safety Monitoring Board (DSMB) appointed by DOD, responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality.

Medical Monitor- Responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of safety reports; resolving safety issues; and interacting with Principal Investigators.
2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Pain is a common consequence of orthopaedic trauma, and previous work has demonstrated that poor postoperative and long-term pain control predicts physical disability, delayed return to work, psychological distress, low satisfaction with healthcare, and failure to participate in physical therapy.\textsuperscript{3-5} Despite increased awareness of the negative consequences of poor pain control, pain care among hospitalized patients remains inconsistent and inadequate.\textsuperscript{6,7} Studies continue to reveal that 50% to 70% of patients experience moderate to severe pain in acute care settings and report insufficient postoperative pain relief.\textsuperscript{8,9} Inadequate postoperative pain management can have several negative consequences. Poorly controlled pain can lead to stimulation of the sympathetic nervous system resulting in tachycardia, and myocardial ischemia in susceptible individuals. Pain can hinder postoperative mobility, impair rehabilitation, and increase the risk of venous thromboembolic disease.\textsuperscript{10} Inadequate pain management can, hence, prolong patient recovery and increase length of hospital stay and health-care costs.

There is now growing recognition that acute painful incidents are often associated with pain that persists and can become chronic.\textsuperscript{13} 30-50% of patients who have acute postoperative pain develop chronic pain that can have major negative effects on quality of life.\textsuperscript{11,12} Importantly, even low levels of persistent pain are associated with decreases in functionality.\textsuperscript{14-16} Several studies have also shown a strong, and potentially etiological, link between pain in the early stages of recovery following traumatic injury and subsequent psychological distress, specifically depression and PTSD.\textsuperscript{2,17} In one study, an increase of one-half standard deviation in hospital pain intensity was associated with a sevenfold increase in the odds of having PTSD at 8 months post discharge.\textsuperscript{2} In another study, pain early in the recovery process following severe extremity trauma was found to be the single largest predictor of long-term chronic pain 5-10 years post injury.\textsuperscript{18} These findings are consistent with the central sensitization model, in which acute pain leads to chronic pain through cellular, molecular and anatomic level changes in pain signaling, which can lead to pain signals being transmitted even in the absence of painful stimuli.\textsuperscript{19} In the Lower Extremity Assessment Project (LEAP) study, pain intensity was found to account for 40% of the variance in overall patient functional outcomes, compared to only 8% for physical impairment.\textsuperscript{20}

A subset of patients who experience orthopedic trauma go on to develop chronic pain in the form of post-traumatic osteo arthritis (PTOA).\textsuperscript{21} PTOA is a disabling condition that results from joint injury. More than 50% of patients with fractures of the distal tibial articular surface develop ankle OA.\textsuperscript{21-26} In one study, 30% of ankles had radiographic evidence of significant PTOA at 2-4 years after a tibial pilon fracture,\textsuperscript{20} and when follow-up was extended to 5-11 years after injury, the incidence had increased to 74%. PTOA is a serious health condition that often leads to substantial pain, disability, loss of work and decreased general health status. OA is the single leading cause of failure to return to active duty after injury in the armed services. Its overall adverse impact on physical and psychological well-being is comparable to that of other major disorders such as stroke, heart disease, or diabetes.\textsuperscript{27} The societal cost of PTOA is high (~$12 billion/year in the U.S.),\textsuperscript{28} since pain and loss of function frequently leads to loss of work capacity. Severe articular fractures most commonly occur in young patients. If PTOA develops,
patients may require reconstructive surgery, including major procedures such as joint fusion or arthroplasty. When performed in a young patient, repeat surgeries throughout their lifetime may be needed to maintain function, further raising the cost, and in some cases resulting in long term disability.

**Current General and Regional Anesthetic Techniques.** Anesthetic technique frequently sets the stage for the postoperative analgesic regimen. Apart from general anesthesia, many regional anesthetic techniques are available, particularly for surgery of the extremities. Regional anesthetic techniques include neuraxial approaches (e.g., spinal or epidural anesthesia), nerve blocks (e.g., brachial plexus, femoral nerve, sciatic nerve), and local anesthetic infiltration of the incision site. Regional anesthetic techniques are frequently combined with general anesthesia, and even when general anesthesia is not used overtly, the deep sedation provided by infusions of intravenous anesthetics and used in conjunction with many regional anesthetic techniques does not functionally differ much from general anesthesia.

Opioids are currently routinely administered during general and regional anesthesia as a component of the anesthetic itself, and to initiate postoperative analgesic therapy. Opioid-related side effects include nausea, vomiting, constipation, pruritis, miosis, sedation, and respiratory depression. All opioids depress respiratory drive depending on dose, patient comorbidities, and other drug therapy. Perioperative treatment for nausea and vomiting includes serotonin uptake inhibitors, corticosteroids, drugs to promote gastric motility, and dopamine antagonists. Constipation is typically treated with stool softeners, and pruritis with antihistamines. Many of these drugs have their own pertinent sets of side effects. Little can be done about miosis, sedation, and respiratory depression except avoid excessive doses of opioid and drugs with synergistic effects. Naloxone can be used to antagonize opioids when their administration has been excessive, but this also reverses the analgesic effects. Beyond these numerous side effects, opioids can also induce opioid tolerance and/or hyperalgesia.

**Multimodal analgesia for perioperative pain management.** Opioid analgesics have been the mainstay of peri-operative pain management. However, the increasing concern for the adverse effects of opioid analgesics, which can impede postoperative recovery particularly in the elderly and ambulatory surgical patients, has led to the concept of multimodal analgesia. The rationale for this approach is that equivalent pain management can be achieved through the additive or synergistic effects of different classes of analgesics, reducing the doses of individual drugs and leading to a lower incidence of adverse effects from any individual medication. A decreased incidence of adverse effects and improved analgesia has been demonstrated with certain multimodal analgesia techniques, resulting in shorter hospitalization times, improved recovery and function, and decreased healthcare costs. Adjuvant drugs that have been studied include nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 inhibitors, alpha-2 adrenergic agonists, steroids, alpha-2-delta receptor modulators such as gabapentin and pregabalin, and N-methyl-D-aspartate antagonists. Of these, Alpha-2 adrenergic agonists such as clonidine and dexmedetomidine have the potential for hypotension, bradycardia, and sedation, and may not be suitable for the trauma patient with acute blood loss. The NMDA antagonist, ketamine, may be associated with excessive sedation and psychomimetic effects, e.g., cognitive dysfunction, hallucinations, and nightmares. The alpha-2-delta receptor modulators and NSAIDs are associated with minimal adverse effects and remain the most promising adjuvant drugs for
perioperative pain management. However, the effectiveness and safety of these agents have not been studied carefully in orthopedic trauma patients.

**NSAIDS for the management of pain following orthopaedic trauma.** NSAIDs are one of the cornerstones of analgesic therapy following a range of orthopedic injuries and surgical procedures. In addition to their analgesic properties, their ability to reduce swelling and inflammation can reduce noxious stimuli and improve mobility. Current data leave little doubt that perioperative NSAIDs can reduce postoperative pain and opioid consumption for many types of surgery in addition to orthopedic surgery. Since the nociceptive signals from the periphery are not limited to the immediate period around the time of injury but continues during the period of tissue injury and inflammation, the optimal pain management should extend beyond the initial period of trauma to the time after the definitive fixation surgery. Hence, in this protocol, anti-inflammatory agents will be initiated soon after the trauma and continued for up to 14 days until the time of definitive surgical fixation of the fracture, and then continued for 48 hours following the procedure or until discharge, whichever occurs first. A recent structured review has identified substantial gaps related to methodology, study size, study population, nature of the intervention, and choice of outcomes. Only 9 of 92 RCTs evaluated were thought to adequately adhere to accepted methodology for analgesic RCTs. Studies of orthopedic procedures other than hip or knee surgery were “scarce.” The hip and knee procedures generally studied were total joint replacements, which usually occur in an older population likely to differ from younger patients. Barely half of the trials were placebo controlled, and only a fraction assessed patient pain intensity more than once in the first 36 hours. Clearly, there is a need for well-conducted, appropriately powered long-term studies of NSAID use in patients undergoing surgery for high energy orthopedic trauma who receive realistic analgesic therapy of more than a single dose.

While the extent of the risk of increased bleeding due to the use of NSAIDs in this population is not known, there is sufficient clinical concern about this issue to warrant additional exploration of NSAIDs that do not reduce clotting. One candidate is meloxicam (Mobic). Meloxicam is a relatively new NSAID which has received particular attention from the military because it has been shown to be more COX-2 selective than other NSAIDs. The majority of the bleeding complications associated with NSAIDs relate to inhibition of COX-1 pathways, particularly platelet function. Several studies have shown that meloxicam does not interfere with platelet mediated hemostasis, does not result in increased bleeding, and has a much reduced inhibition of platelet function when compared to nonspecific NSAIDs. These properties are likely the reason for the lower levels of complications observed in a review of over 5000 clinical trial patients who received meloxicam versus nonspecific NSAIDs. This improved safety profile has led the U.S. Army to adopt meloxicam as the NSAID of choice for combat soldiers who would otherwise be placed at too high a risk of bleeding with this class of drugs. The profile of this drug has led to its selection for off-label usage in this protocol during the period between acute injury and definitive fixage.

Perioperatively, NSAIDS are used extensively, most often as a component of a multimodal analgesic regimen, to treat the pain and swelling that accompanies orthopedic injury and as components of perioperative analgesic regimens following orthopedic surgery. Noxious input during wakefulness or under general anesthesia initiate a cascade of peripheral and central
nervous system events that increase sensitivity to noxious stimuli and can lead to allodynia and hyperalgesia. Apart from modulating the peripheral inflammatory response to tissue injury, NSAIDs can modulate the neurobiologic cascade that leads to hyperalgesia since both COX-1 and COX-2 play essential roles in the peripheral and central aspects of the neural response to noxious input. Therefore, as an intravenous nonspecific COX antagonist, ketorolac is ideally suited to limit this process in the perioperative period. Ketorolac is indicated for short-term (up to 5 days in adults) management of moderately severe acute pain requiring analgesia at the opioid level, and is particularly advantageous in the perioperative period because its intravenous formulation permits administration throughout surgery and postoperatively, regardless of the ability to ingest oral medication.

**Gabapentinoids for the management of pain following orthopaedic trauma.** Gabapentin, developed as an anticonvulsant drug, has been FDA-approved for the treatment of postherpetic neuralgia and recommended as a first line drug for neuropathic pain. Additionally, it has a not yet fully defined niche in the treatment of acute perioperative pain. Its potential role in managing pain of orthopedic origin is suggested by studies in animal models of inflammatory pain and acute arthritic pain. A newer analog, pregabalin, has also been shown to be effective in the management of many chronic pain states and approved in the U.S. for use in postherpetic neuralgia, painful diabetic neuropathy and fibromyalgia. In the last 4 years, 22 RCTs have investigated the potential benefits of gabapentin in postoperative pain management in over 1900 patients and eight studies have also examined the effects of pregabalin in about 700 surgical patients. Meta-analysis and critical reviews conclude that gabapentin and pregabalin provide better post-operative analgesia than placebo. In addition, gabapentin and pregabalin reduced opioid consumption in the first 24 hours post-surgery by 20% to 62% or by 25-30 mg of morphine. Other suggested advantages of gabapentinoids include reduction in the incidence of anxiety, sleep disturbance and delirium as well as enhanced early postoperative joint mobility. However, there are several evidence gaps. Most of these studies include small numbers of non-orthopedic surgical patients who were followed during the immediate postoperative period (up to 7 days). In only half of the studies was pain evaluated with movement and only 7 gabapentin studies followed patients from 1-3 months post-surgery. Most studies included patients undergoing abdominal hysterectomy, laparoscopic abdominal procedures or thoracotomy. Only two RCTs with pregabalin included patients undergoing elective orthopedic surgeries. Gabapentinoids have multiple targets, but their effects on pain are generally considered to be due to the inhibition of Ca2+ currents via high-voltage-gated channels, resulting in reduced neurotransmitter release by pain signaling fibers and decreased post-synaptic excitability. Decreased Ca2+ influx may also lead to suppression of neuronal excitability following nerve or tissue injury. However, gabapentinoids have minimal effects on normal pain signaling and their effects on pain occur primarily in the setting of sensitized neurons. The profile of this drug has led to its selection for off-label usage in this protocol during the period between acute injury and definitive fixation and for up to 48 hours following definitive fixation.

**2.2 Rationale**

Despite the importance of controlling postoperative pain, pain management approaches for orthopedic trauma patients remains inconsistent and often inadequate. Studies continue to indicate that patients experience moderate to severe pain in acute care settings and insufficient
pain relief post-operatively. Preoperative and perioperative pain management using non-steroidal anti-inflammatory drugs (NSAIDs) such as ketorolac and meloxicam, and more recently, anticonvulsants such as pregabalin, has been found to substantially improve post surgical pain control in numerous settings. However, this type of pain management has not been widely used in orthopaedics because of conflicting data about increased risk of nonunion, wound closure and bleeding complications. Given the central role of pain management in the etiology of long-term disability following trauma, it is critical to definitively resolve this question in the context of a randomized clinical trial. This study focuses on isolated extremity trauma (many of whom have a single surgical encounter), but our findings should be easily extended to poly-trauma populations. A critical next step in our research agenda will be to test the results of this study in a pragmatic trial in which multimodal perioperative pain management is the standard for all surgical encounters in the care of the multiply injured patient.

The patients to be included in the Pain study with ankle fractures are at increased risk for the development of PTOA. Continued refinement of existing treatment methods for the repair of the pilon fractures has not resulted in changes to the substantial incidence and severity of PTOA, and there are knowledge gaps in the understanding of the development of this condition. It is believed that the severity of the joint injury and the elevated contact stress challenge after treatment are influential mechanical factors, but these were previously unmeasurable. Work by the University of Iowa Center of Research Translation (UI CORT) elucidating PTOA pathogenesis has resulted in the development of novel techniques to objectively quantify these mechanical factors. In a prospective single-center study of tibial pilon fractures, patients stratified using the resulting metrics demonstrated threshold levels of fracture severity and of contact stress challenge, above which subsequent PTOA was nearly inevitable. Since the completion of that study, highly expedited methods for obtaining these metrics have been developed, providing the capability to routinely make these assessments in hundreds of patients. Therefore, there is an opportunity to conduct a pilot study drawing from the Pain study population, testing the application of these metrics to data from multiple sites, in addition to furthering our understanding of the relationships between fracture severity, contact stress, chronic pain, and the development of PTOA. The data from this and future studies using these techniques will allow surgeons to assess risk for PTOA, which will provide clinically relevant information to be used in patient treatment.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The risks associated with this study primarily concern adverse reactions to the study drugs. All drugs are FDA approved and marketed for a variety of uses (see section 2.1). The proposed protocol is of an investigational use of the medications meloxicam and pregabalin in a new clinical setting, and ketorolac for an indicated usage. In accordance with 21 CFR 312.2, this study meets IND Exemption requirements. An application for an IND exemption was approved by the FDA for the proposed indications outlined in this protocol. The intention of the protocol is not to support a new indication for use or significant change in labeling of the drugs; is not intended to support a change in advertising for the drugs; will not test a new route of administration or dosage of the drug, nor is it being used in a new clinical population; and the
study will be conducted with informed consent and in compliance with 21 CFR 312.7 regarding promotion and sale of drugs. Patients in the study will be actively monitored for any adverse reactions (See Appendix E).

**Side Effects of Ketorolac.** Concerns about renal impairment, gastrointestinal irritation, and platelet inhibition constrain usage and limit the dose and duration of ketorolac administration. Typical intravenous doses for young adults (≤65 years of age) are 30 mg every 6 hours for 48 hours, which is the dose proposed in this trial. It is recommended by the manufacturer that this dose not be exceeded for each 24 hour period, be limited to no more than five days of IV, IM and oral therapy, and that this dose should be halved for elderly patients, those with renal impairment, and patients weighing less than 50 kg (ketorolac package insert, 2009). Applying this limitation appears to have substantially reduced some of the complications first reported with the introduction of ketorolac. See Section 9.6 for reduced dosing considerations. Common and infrequent side effects of ketorolac are summarized in Appendix E. More directly relevant to orthopedics, in animal models, NSAIDs in general and ketorolac in particular are known to impair osteogenesis. The effects for these drugs, however, are reversible after short-term treatment. Similarly, animal studies with chronic ketorolac administration raise concern with respect to the strength of healed wounds, with variable results for muscle and ligamentous injury. In human studies of spinal fusion, 48 hours of ketorolac therapy for a total dose of 240 mg appears not to affect the fusion rate, but longer duration therapy, even at lower doses may be problematic. However, in a fracture model with young mice, a variety of COX antagonists did not affect long-term tibial healing, consistent with a similar observation in young patients undergoing scoliosis surgery. These studies also indicate that smokers and older patients appear to be at greater risk of nonunion. Since relatively little is known about the impact of NSAIDs on clinical bone healing, other than the limited, largely retrospective, data on spinal fusion, or wound healing in general, this will be examined as one of the primary research questions of the current study.

**Side Effects of Meloxicam:** While all NSAIDs share a similar side effect profile, meloxicam has been shown to have a substantially lower risk than other drugs in this class. Common side effects include upset stomach, nausea, drowsiness and diarrhea. Other, infrequent side effects are summarized in Appendix E. A review of over 5000 clinical trial participants showed meloxicam has no increased rate of any side effects when compared to other NSAIDs, but significantly lower rates of gastrointestinal side effects, bleeding complications, dyspepsia, abdominal pain, perforations and ulcerations.

**Side Effects of Gabapentinoids:** Relative to opioids and NSAIDS, gabapentinoids have few side effects, the most common including somnolence and dizziness. Headaches, coordination problems, peripheral edema, blurred vision, and gastrointestinal symptoms have also been reported. Common and infrequent side effects for pregabalin are listed in Appendix E.

**PTOA Pilot study:** There should be no additional risks associated with participation in the expanded PTOA part of the study, as patients will be followed and treated through standard-of-care. For the 60 patients selected to receive an additional CT scan, the additional risk will be communicated as part of the consent process. CT scans are routinely obtained to evaluate a number of musculoskeletal conditions. Since CT scans expose patients to the greatest amounts of
radiation of all imaging modalities, the physician must be cognizant of the effective doses of radiation that are administered. However, according to a 2009 study in the Journal of Bone and Joint Surgery, the amounts of radiation emitted during CT examinations of distal structures such as the ankle are essentially negligible. In fact, an individual may be subjected to more radiation as a result of a round-trip airplane flight from New York to London (0.1 mSv) than with a CT examination of the ankle (0.07 mSv).

2.3.2 Potential Benefits

This study presents possible benefits of improved pain management for patients who are randomized to one of the treatment arms of the study. While patients in the placebo arm of the study and in the expanded PTOA study may not accrue any direct benefits as a result of their participation in this study, participation may help determine the best treatment for similar fractures in the future.

3. STUDY OBJECTIVES

3.1 Primary Objective

Specific Aim 1: Evaluate the effect of standard pain management (Group 1) vs. standard pain management plus pre and peri-operative NSAIDs (Group 2) in the treatment of severe limb fractures.

Hypothesis 1a: When compared to patients who received standard of care pain management, patients treated with NSAIDs will: (1) have reduced post operative opioid utilization; (2) report reduced levels of persistent pain; and (3) have noninferior rates of surgery for nonunion.

Hypothesis 1b: When compared to patients who received standard of care pain management, patients treated with NSAIDs will benefit from (1) improved post operative pain control; (2) improved pre operative pain control; (3) reduced lengths of stay; (4) reduced pain interference; (5) improved functional outcomes; (6) lower levels of depression and post-traumatic stress disorder (PTSD); (7) improved overall health status; and (8) have noninferior rates of analgesic treatment related side effects.

3.2 Secondary Objectives

Specific Aim 2: Evaluate the effect of standard pain management (Group 1) vs. standard pain management plus pre and peri-operative pregabalin (Lyrica) (Group 3) in the treatment of severe limb fractures.

Hypothesis 2a: When compared to patients who received standard of care pain management, patients treated with pregabalin will: (1) have reduced post operative opioid utilization; (2) report reduced levels of persistent pain; and (3) have noninferior rates of surgery for nonunion.
Hypothesis 2b: When compared to patients who received standard of care pain management, patients treated with pregabalin will benefit from (1) improved post operative pain control; (2) improved pre operative pain control; (3) reduced lengths of stay; (4) reduced pain interference; (5) improved functional outcomes; (6) lower levels of depression and post-traumatic stress disorder (PTSD); (7) improved overall health status; and (8) have noninferior rates of analgesic treatment related side effects.

Specific Aim 3: Estimate the incremental cost effectiveness of each adjunctive analgesic therapy relative to standard of care analgesic therapy in the treatment of severe limb fractures. Costs will be estimated from both the health care provider perspective and the societal perspective. The time horizon for cost-effectiveness analysis will be based on the actual period of observation (12-24 months). Incremental cost-effectiveness ratios will be calculated for: (a) study group 2 (NSAIDS) relative to standard of care; and (b) study group 3 (pregabalin) relative to standard of care. For purpose of cost-effectiveness analysis, effect will be measured as unit change in specific outcome metrics at 12 months (or longer period as available) compared to baseline. The following cost-effectiveness metrics, all relative to standard of care, will be reported:

- incremental cost per unit change in the Brief Pain Inventory
- incremental cost per unit change in the Short Muscular Function Assessment (SFMA)
- incremental cost per unit change in health state preference (“utility”) as derived from the VR-12

PTOA Pilot Study: Additional funding was received from NIH to conduct a pilot, observational study of post-traumatic osteoarthritis (PTOA), leveraging current resources of the Pain study. PTOA is an important outcome in the population to be enrolled in the Pain study. The aims of the PTOA Study are to: (1) measure the incidence of PTOA and chronic pain for up to 24 months following fracture reduction surgery and (2) quantify the extent to which fracture severity and post-reduction contact stress are related to the development of PTOA. Accomplishment of these aims will require (1) for all patients in the Pain study: complete a PTOA survey at 12 months and at any subsequent visits that are conducted as part of standard of care and provide access to all standard of care imaging studies completed during the study period and (2) for a subset of 60 pilon fracture patients enrolled in the Pain study for whom post-operative CT scans are not standard of care, obtain additional consent for completion of a study-funded post-operative CT scan up to 3 months following definitive fixation, and 24 month radiographic study.

4. STUDY DESIGN

4.1 Description of the Study Design

The proposed study is a three arm, double blinded, randomized, placebo controlled multicenter Phase III clinical trial. The objective of this study is to definitively resolve questions regarding the use of multimodal pharmacologic pain management for orthopedic trauma patients in the context of a multicenter, randomized clinical trial. We will test whether adjunctive analgesic therapy during the pre and peri-operative period, in addition to standard of care pain management, can improve overall pain control and pain related outcomes without increasing analgesic related side effects. In addition, a significant proportion of this population develops
chronic PTOA. A sub-objective of this study is to conduct a pilot study examining the relationships between fracture severity, contact stress, and the subsequent development of PTOA in this population.

Figure 1, below, provides a graphical representation of the main study procedures.
4.2 Study Endpoints

4.2.1 Primary Endpoint
All patients will be followed through 12 months following injury.

4.2.2 Secondary Endpoints - NA

4.2.3 Exploratory Endpoints - NA

4.2.4 Pilot study Endpoints
For any patients for whom it is standard of care to have clinical follow up beyond 12 months, we will follow for up to 24 months following definitive fixation. A subset of patients in the PTOA pilot study (n=60) will be consented and complete their final study follow up visit at 24 months following definitive fixation.

5. STUDY POPULATION

5.1 Description of the Study Population
Inclusion and exclusion criteria were developed to select a study population of patients with orthopaedic trauma known to experience moderate to high rates of chronic pain and nonunion: patients with fractures to the ankle and midfoot, the tibia, the humerus, and the femur. Since military combat injuries are typically thought of as open, we will include Grade I/II and III open fracture types in our study. However, since post surgical pain is not limited to open fractures, and the concept of perioperative pain management should apply to both open and closed injuries, we will also include closed versions of these high-energy injuries in our study population.

5.1.1 Participant Inclusion Criteria
1. Patients with one of the following types of injuries:
   a. Unilateral, Grade I &II open or closed pilon (distal tibial plafond), calcaneus, talus fractures and Lisfranc dislocations requiring operative treatment with fixation; or
   b. Unilateral, open (type I, II, or IIIA) ankle fractures with associated dislocation on presentation (OTA 44B3 or 44C) requiring operative treatment with fixation; or
   c. Unilateral, open or closed distal and proximal humerus (OTA 11A-C and OTA 13 A-C); or
   d. Open femoral shaft fracture (OTA 32 A-C; Gustilo Type I-IIIC) or open or closed supracondylar femur fractures (OTA 33 A-C); or
   e. Open or closed tibial plateau or shaft fractures (OTA 42 A-C or 43 A-C)
2. Any combination of the above injuries which are surgically treated as a wholePatients who present to the admitting hospital or clinic, either acutely or following an initial
assessment in the Emergency Department, for care up to 10 days following initial injury
3. Patients 18-80 years old inclusive.
4. Patients who are English or Spanish competent.
5. Treating physicians agree that none of the study drugs are indicated for standard of care treatment for this patient.
6. Patients able to be followed at the METRC facility for at least 12 months following injury

5.1.2 Participant Exclusion criteria

1. Patient unable to provide informed consent
2. Patients with chronic pain being presently treated with opioid or gabapentinoid prescription or any other alternative therapy.
3. Patients who are current IVDA
4. Patients with bilateral or ipsilateral injuries requiring surgery
5. Patients with other orthopedic or non-orthopedic injuries requiring operative intervention
6. Patients with severe osteopenia.
7. Patients who are skeletally immature (defined as less than 18 years of age or no radiographic evidence of epiphyseal closure).
8. Patients who are expected to have a post-surgical stay less than 24 hours.
9. Patients with a history of allergy to any drugs in the study.
10. Patients unable to swallow oral medications or without adequately functioning GI tract.
11. Patients with a history of gastrointestinal bleeds or gastric perforation.
12. Patients currently receiving an aspirin or NSAID regimen (exception: low dose aspirin, 81mg).
13. Patients with any bleeding disorders.
14. Patients with severe renal failure. Patients with moderate renal failure may participate in the study at a modified dose. See Section 9.6.
15. Patients undergoing daily treatment with systemic glucocorticoids before surgery.
16. Patients using angiotensin-converting enzyme (ACE) inhibitors, who may be at increased risk of developing angioedema with pregabalin.
17. Patients likely to have severe problems maintaining follow-up, including patients diagnosed with a severe psychiatric conditions, patients who live too far outside the hospital’s catchment area, patients who are incarcerated and patients who have unstable housing situations.
18. Patients who experienced a loss of consciousness consistent with a clinical diagnosis of a closed head injury, or concern of a cerebrovascular bleed secondary to traumatic brain injury.
19. Patients with a GCS <15
20. Patient speaks neither English nor Spanish.
21. Patients who are pregnant or lactating at time of screening

5.1.3 Co-Enrollment Guidelines
This study will follow METRC co-enrollment guidelines. Co-enrollment in other randomized clinical trials where randomization occurs during the index hospitalization (sponsored by METRC or another sponsor) is not allowed. Co-enrollment in other observational studies is permitted depending on local IRB guidelines.

5.2 Strategies for Recruitment

5.2.1 Recruitment Overview

Patients will be screened and enrolled in each center by the local research coordinator in close coordination with the surgeon co-investigators. Patients will be enrolled upon presentation during the first 48 hours following admission to the index hospital or at the first clinic visit prior to definitive fixation if they were initially seen and discharged from the Emergency Department. The procedures are summarized here. The study coordinators monitor the in patient census of orthopaedic patients to look for patients who are potential inpatient Pain study candidates and will review orthopaedic consultations to the Emergency Department to look for potential patients who will be going to the clinic prior to fixation. The study coordinators initiate the discussion regarding the study and the attending surgeon is involved at the time of consent. Patients will be provided a METRC brochure (Appendix I) and study summary as recruitment materials. A video describing Pain study treatment and procedures (Appendix J) will be provided to assist with the recruitment process. Patients who decide to participate in the Pain study will provide consent to be randomized to a treatment arm, and to allow investigators access to all radiological films made as part of standard of care up to 24 months following definitive fixation (Appendix F). As part of this consent, patients will indicate whether they are willing to be approached following definitive fixation and offered the opportunity to participate in the PTOA pilot study. This secondary consent could be up to three months following their injury. The PTOA pilot study will consist of an additional CT scan following definitive fixation and one follow-up radiographic study 24 months following definitive fixation. Consenting patients will be approached following definitive fixation, which typically occurs up to 3 months after their injury, to provide consent for the PTOA pilot study (Appendix G). All participants will be offered nominal compensation for participation in the main study and the pilot study. A payment will be made upon return of the empty blister pack and at each follow-up visit. Patients will be asked to sign an IRB approved consent form (Appendix F or G), and will be given a copy to keep. The Coordinating Center will be available to help adjudicate eligibility.

5.2.2 Identifying patients eligible for the PTOA pilot study

A subset of enrolled patients with pilon fractures who do not receive a CT scan following definitive fixation will be prospectively identified and included in the PTOA pilot study, regardless of Pain treatment group. Each patient enrolled in the Pain study will be assessed for potential enrollment into the PTOA pilot study based on:

- Whether or not the patient experienced a pilon fracture;
- Confirmed negative pregnancy test
- Severity of the fracture. We will select cases in the mid range of severity, as patients with severe injuries are more likely to receive CT scans as normal SOC therapy.
6. STUDY TREATMENTS

6.1 Description of the Study Treatment Arms: Main Pain Study

In this study, patients for whom one of the study drugs is indicated as standard of care therapy would be excluded from participation. Randomization to a study treatment arm will proceed only when the treating physician has ascertained that none of the study drugs would be standard of care first line treatment for the patient’s pain.

The online Data Management System maintained at the Coordinating Center will randomize patients electronically (See Figure 2). Block randomization will be used to ensure equal distribution of treatment and control patients across the fracture types and within each center. Patients will be randomly assigned (within each block) in a 1:1:1 ratio to either of two treatment groups or control group. Participants who refuse randomization will not be eligible for the study and will receive the standard of care for pain management. Cross over from one treatment arm to another should be extremely rare in the hospital setting, and should only occur in the unlikely case where the surgical team determined oral or intravenous drug could not be provided at all, or if the medication is not available prior to surgery due to coordination error. Cross over to the NSAID arm could conceivably happen while the patient is at home and self-medicates with oral NSAIDs. Patients will be provided with clear instructions on their blister pill pack (Appendix K) regarding the potential dangers of doing this and will be advised not to take any oral NSAIDs during this period. As patients and clinicians will not know which treatment group the patient is in, there is no chance that they will elect to switch groups based on the result of the randomization.

Safety Monitoring: Because the non-inferiority of the multimodal pain management compared to usual care is an explicit outcome of the study, common adverse effects and complications will be assessed through a daily log completed by the patient listing common adverse reactions, including somnolence, dizziness, headaches, and other central nervous system effects, peripheral edema, visual changes, and dry mouth (See Appendix E) and by a clinical survey of symptoms to include excessive bleeding, thrombocytopenia, and anemia, during the index hospitalization and at discharge from additional surgical admissions up to definitive fixation. Using the table in Appendix D, each reported AE will graded 1-4 and reported to the MCC and locally according to IRB reporting requirements. See Section 9 for definitions and reporting requirements for AEs and SAEs related to the use of study medications. Long term potential adverse events, such as nonunion, will be assessed as part of the clinical follow up. Patients will be followed for these events up to one year.

6.1.1 Group 1: Standard pain management plus preoperative oral placebo plus perioperative intravenous placebo and oral placebo

This group will serve as the control group. Patients will take an oral placebo pill twice daily for the first 14 days after enrollment into the trial, which will be dispensed from a pre-packaged blister pack. The blister pack oral medications will be suspended any time the patient...
experiences a surgical procedure. For all surgical procedure, up to and including definitive fixation, the patient will receive medications according to a perioperative protocol. The perioperative protocol will include an oral dose of placebo up to one hour prior to surgery and twice daily for up to 48 hours following any surgery, in addition to an intravenous dose of placebo up to one hour prior to surgery and every 6 hours for up to 48 hours following surgery. For any surgery except definitive fixation, the oral blister pack medications the patient would have taken during those 48 hours will be wasted by the research pharmacy, and 48 hours following the procedure (or at the time of discharge, if applicable), the patient will return to the oral blister packaged medication protocol until the next procedure, definitive fixation, or the end of the blister pack, whichever comes first. Any medication remaining in the blister pack following definitive fixation should be wasted according to local pharmacy protocol. Patients classified as renal compromised will receive a halved dose of all placebo (See Section 9.6 for reduced dosing procedures). Labeling on the package and generated by REDCap inclusion criteria will serve as reminders of the alternate dosing strategy. Oral placebo will consist of size 3 capsule shells backfilled with Avicel and then over-encapsulated with AA capsule shells, which will, in turn, be backfilled with more Avicel. All placebo preparations by Fisher Clinical Services (Bristol) LLC, 406 Crossings Dr, Bristol, PA 19007.

Should a patient be admitted for an interim surgery between the time of study initiation and definitive fixation, the patient will receive the IV placebo and oral placebo up to one hour prior to and for up to 48 hours following the surgery, or until the patient is discharged.

6.1.2 Group 2: Standard pain management plus preoperative oral meloxicam plus perioperative intravenous ketorolac and oral placebo

In addition to SOC pain management, patients randomized to the NSAID group will receive an oral 7.5 mg dose of Meloxicam (Meloxicam 7.5 mg tablets, NDC 68382-000-01; manufacturer: Zydus; encapsulated in size AA empty capsule shells, backfilled with Avicel by Fisher Clinical Services (Bristol) LLC, 406 Crossings Dr, Bristol, PA 19007) twice daily, to be initiated on enrollment and continued for 14 days or through definitive fixation, whichever comes first. The proposed dosing schedule represents the maximal safe dose of an adult population. The Meloxicam will be dispensed from a pre-packaged blister pack. The Meloxicam will be suspended any time the patient experiences a surgical procedure. For all surgical procedures, up to and including definitive fixation, the patient will receive medications according to a perioperative protocol. The perioperative protocol will entail 30 mg of intravenous (IV) ketorolac (Ketorolac 30 mg/ml dose vial, NDC 00409-3795-01; manufacturer: Hospira) administered up to one hour prior to the procedure and every 6 hours for up to 48 hours following the procedure. In addition, as part of the perioperative protocol, patients will receive an oral dose of placebo up to one hour prior to the procedure and every 12 hours for up to 48 hours following the procedure.

The proposed dosing schedule of 30 mg IV Ketasol up to one hour prior to the procedure and every 6 hours for up to 48 hours following procedure represents the maximal generally accepted safe dose of ketorolac currently in use for orthopedic surgery. Limiting ketorolac therapy to 48 hours is motivated primarily by data on bone healing which suggests that more prolonged NSAID therapy will lead to nonunions. However, these data are largely from retrospective
studies of modest size and limited to spinal fusion. The current study will address the question of bone healing prospectively in a large population of trauma-related orthopedic procedures. This dosing regimen will be altered for patients age of 65 and up and with known renal insufficiencies (assessed by BUN/Creatinine values – See Section 9.6). The dose will be halved for these patients, and the patient will only receive \( \frac{1}{2} \) the dose dispensed by the pharmacy. Labeling on the package and generated by REDCap inclusion criteria will serve as reminders of the alternate dosing strategy.

**6.1.3 Group 3: Standard pain management plus preoperative pregabalin plus perioperative intravenous placebo and oral pregabalin**

In addition to SOC pain management, patients randomized to the pregabalin group will receive an oral 75mg dose of pregabalin twice daily (Lyrica 75 mg tablets, NDC 00071-1014-68; manufacturer: Pfizer; encapsulated in size AA empty capsule shells, backfilled with Avicel by Fisher Clinical Services (Bristol) LLC, 406 Crossings Dr, Bristol, PA 19007; Lyrica 300 mg tablets, NDC 00071-1018-68; manufacturer: Pfizer; encapsulated in size AA empty capsule shells, backfilled with Avicel by Fisher Clinical Services (Bristol) LLC, 406 Crossings Dr, Bristol, PA 19007; Lyrica 300 mg tablets, NDC 00071-1018-68; manufacturer: Pfizer; encapsulated in size AA empty capsule shells, backfilled with Avicel by Fisher Clinical Services (Bristol) LLC, 406 Crossings Dr, Bristol, PA 19007;), to be initiated on enrollment and continued for 14 days or through definitive fixation, whichever comes first. The recommended initial daily dosing of pregabalin is 150 mg a day in two or three divided doses. We have chosen to use a 75 mg twice daily dosing based on studies that suggest that this dose is effective and well tolerated in similar populations our experience with this drug in patients with chronic pain.\(^4\)\(^4\) The pregabalin will be dispensed from a pre-packaged blister pack. The pregabalin dispensed from the blister pack will be suspended any time the patient experiences a surgical procedure. For all surgical procedures, up to and including definitive fixation, the patient will receive medications according to a perioperative protocol. The perioperative protocol will entail an oral bolus dose of 300 mg of pregabalin up to one hour prior to the procedure and a 75 mg dose every 12 hours for up to 48 hours following the procedure. In addition, as part of the perioperative protocol, patients will receive an IV dose of placebo up to an hour prior to the procedure and every 6 hours for up to 48 hours following the procedure.

Prior studies with pregabalin have used either a single dose preoperatively,\(^4\)\(^4\)\(^–\)\(^6\)\(^5\) or two doses 12 hours apart,\(^6\)\(^6\) where the two most commonly used doses have been 150 or 300 mg. We have chosen the 300 mg preoperative dose based on the positive study in orthopedic patients that showed a nearly 50% reduction in opioid consumption in the first 24 hours post surgery.\(^4\)\(^4\) Since pain associated with major trauma is likely to last longer than the other surgical conditions in which the beneficial effects of pregabalin have been tested, the drug treatment will be continued for up to 48 hours following definitive fixation, or until discharge, if the patient is discharged less than 48 hours following the fixation. This dosing regimen will be altered for patients age of 65 and up and with known renal insufficiencies (assessed by BUN/Creatinine values – See Section 9.6). The dose will be halved for these patients, and the patient will only receive \( \frac{1}{2} \) the dose dispensed by the pharmacy. Labeling on the package and generated by REDCap inclusion criteria will serve as reminders of the alternate dosing strategy.
Figure 2: Medication Dosing

Screen High Energy Orthopedic Trauma

- Meets inclusion criteria

Enroll and Randomize to Treatment Group + SOC Therapy

Group A: Placebo
- Oral Placebo; up to 2 wks

Group B: NSAID
- Oral NSAID (Meloxicam 7.5 mg po bid); up to 2 wks

Group C: Gabapentinoid
- Oral Gabapentinoid (Pregabalin 75 mg po bid); up to 2 weeks

If the patient experiences a surgical procedure prior to the definitive fixation (e.g. calcaneal fracture repair, or fibular and/or spanning external fixation), suspend oral therapy and initiate perioperative adjunctive analgesic therapy; otherwise PO therapy for up to 2 weeks, or through definitive fixation

Oral Placebo + IV Placebo Therapy up to 1 hour prior to surgery and for 48 hours, or until resumption of oral therapy

Oral Placebo + 30 mg IV ketorolac up to 1 hour prior to surgery and q6h post procedure for 48 hours or until resumption of oral therapy

IV Placebo + 300 mg pregabalin po up to 1 hour prior to surgery and 75 mg po bid post procedure for 48 hours or until resumption of oral therapy

Definitive Fixation – Measure opioid utilization for up to 48 hours post operatively

Oral Placebo + IV Placebo Therapy

Oral Placebo + 30 mg IV ketorolac up to 1 hour prior to surgery and q6h for 48 hs post procedure

IV Placebo + 300 mg pregabalin PO up to 1 hour prior to surgery and 75 mg PO bid post procedure for 48 hrs
6.2 Study Agent Administration: Main Pain Study

Medications will be provided through research pharmacies at each site. Medications will be dispensed by a research pharmacy in two forms. Each participant will begin medication dosing using a 14-day blister pack containing either two daily doses of placebo, Meloxicam, or pregabalin that will be initially administered at prescribed intervals. If the patient is discharged prior to definitive fixation, the patient will go home with the blister pack and continue to take the study medications in addition to any standard of care prescriptions until readmission for definitive fixation or until reaching the end of the blister pack, whichever comes first. Patients will be provided with a brochure providing instructions on how to take the medications from the blister pack and record administration (Appendix L).

At the time of any surgical procedure up to and including the definitive fixation, the research pharmacy will dispense the surgical medications, which will contain IV ketorolac and oral pregabalin or placebo. These medications will be administered during the period before and after surgery, according to the schedule described in section 6.1 and detailed in Figure 2. The oral medications from the blister pack will be suspended during this peri-operative period.

6.3 Concomitant Medications and Procedures: Main Pain Study

Patients participating in this study may receive normal, standard of care treatment for their injury and for pain management, with the exception of use of medications noted in section 6.5.

6.4 Assessment of Participant Adherence with Study Agent(s)/Intervention(s): Main Pain Study

Adherence to the study intervention will be assessed through the participant completion of blister pack packaging log (Appendix K) and the empty blister pack participants will be asked to return to the study coordinator on admission for the definitive fixation of their fracture. Adherence to medication administration during the inpatient phase of the study will be assessed through chart abstraction.

6.5 Precautionary and Prohibited Medications and Procedures: Main Pain Study

Patients will not be permitted to take gabapentin or its analog, pregabalin outside of their study medication. No NSAIDs will be prescribed and the patient instructed to avoid over the counter medications such as aspirin, Aleve, Advil, etc. (Exception- patients on low dose aspirin 81 mg for prophylaxis may continue to take it perioperatively along with study medications following the usual practice of the treating physician Other medications known to interact with agents used in the study will be modified in accordance with standard of care by the treating physician.

6.6 Prophylactic Medications and Procedures N/A

6.7 Rescue Medications N/A

7. STUDY PROCEDURES/EVALUATIONS
7.1 Clinical Evaluation

7.1.1 Medical Record Review

From the medical record, the study coordinator will abstract information needed to characterize the patients’ injuries, baseline comorbidities and concomitant medications at the start of the study. These data are part of the METRC standard dataset. Additionally, the study coordinator will abstract opioid utilization during the inpatient periods of the study as well as prescriptions written for pain management at discharge. Finally, the medical record will serve as an additional source of information for completing the complication log.

7.1.2 Medication Packaging/Study Log (Appendix K)

Upon enrollment into the study, patients will be provided with a blister pack of pills, imprinted with spaces for recording information about their experience using study medications. Enrolled patients will be instructed to record morning and evening pain score at the time they take their medications, using a numeric rating scale as well as the time they took their morning and evening dose of medication. Additionally, packaging will provide an opportunity to record any side effects associated with use of the medications. These logs will be used from enrollment through admission for definitive fixation, at which point they will be collected by the research coordinator for up to 48 hours after definitive fixation.

7.1.3 Patient Interview

All data collected as part of the Pain study and the PTOA pilot study will be through the use of standardized instruments. A list of these instruments and the timing of their administration can be found in Appendix C. Patients will complete a baseline interview during their initial hospitalization. At this time, baseline demographic information will be collected, in addition to measures of pain.

While hospitalized, the patients will be assessed daily for pain as well as any side effects and opioid use they may be experiencing while on the study drug regimen.

Participant pain will be assessed at the 3 month post injury SOC follow-up visit. Participants will complete interviews at 6 and 12 months post injury, at which point they will respond to questions regarding pain, pain interference, osteoarthritis, function (6 and 12 months), PTSD (12 months) and depression (12 months). Finally, all patients routinely seen after 12 months and the subset of the 60 patients in the PTOA pilot study completing the 24 month assessment will be assessed for osteoarthritis using the AOS. All follow up interview intervals assume a window of two weeks prior to and following the scheduled date.

7.1.4 Radiographs and CT Scans: PTOA Pilot Study Data

All patients participating in the study will provide consent for de-identified copies of any image studies (e.g. radiographs, CTs, etc) made as part of SOC activities to be forwarded to the University of Iowa for analysis, where the principal investigator for the PTOA pilot study will
oversee reading and analysis. A subset of patients with pilon fractures recruited at sites where post-operative CT scans are not the standard of care will be recruited into the PTOA pilot study (see section 5.2.2). These patients will receive a CT scan, paid for by the study, following definitive fracture reconstruction, up to three months following the study injury. The images obtained from both groups will be used to assess fracture severity and chronic contact stress challenge, using existing expedited computational stress analysis methods.

Radiographs: The standard AP, lateral, and mortise view radiographs of the patient’s injured ankle routinely taken as part of clinical care will be obtained at the time of injury and after each surgical intervention for all patients in the Pain study. These radiographs will be used initially by the study team to classify the fractures, and at follow-up to assess outcome. The timing of these radiographs will follow standard of care, and are routinely taken at the time of initial hospital evaluation, immediately following treatment, and at 6, and 12 months after injury (per standard of care). The standard of care images taken on patients who are routinely followed beyond 12 months will be collected at each follow-up visit through 24 months. For the 60 patients in the PTOA pilot study, final radiographs will be taken at 24 months after definitive fixation to assess for evidence of PTOA. All radiographs obtained beyond 6 months after injury will be taken in the weight bearing position.

CT scans: For each patient, standard of care CT scans will be obtained, and these will be used to measure fracture severity. In severe fractures, this study will often be obtained after the application of a temporary joint-spanning external fixator. Thus, the fracture severity analysis will be based on fractured distal tibias with limb alignment provisionally controlled (as needed). After definitive fracture reconstruction, some patients, depending on the standard practices at the treating facility, will receive a second CT scan will be obtained for assessment of chronic contact stress challenge. When this occurs, the study will obtain these CTs. For the 60 patients in the PTOA pilot study, post operative CT scans will be taken as a study procedure, to assess for contact stress challenge.

While the study will not rigidly prescribe CT acquisition protocols given these protocols are largely standard of care, we provide here some basic guidance. The fractured extremity of patients should be scanned in the transverse plane (i.e., with the X-ray beam perpendicular to the long axis of the tibia). Helical CT spatial resolutions on the order of 0.6 mm slice thickness × 0.3 mm reconstruction interval, with a 512×512 pixel image matrix and a field of view (on the order of 24 cm) to provide in-plane spatial resolutions of 0.3×0.3 mm. Typical scanning parameters would be 120 kVp, 75 mAs, 0.5-second gantry rotation, 3.5-mm table travel per rotation. A standard bone reconstruction algorithm should be suitable.

Image transfer: There are challenges in developing image transfer techniques as part of a multi-institutional research effort, beginning with the variance in image devices, imaging protocols, file formats and data transfer standards across facilities. Though image files are likely to not be of proprietary format, how sites manage them is likely to vary, which could affect access and exporting. Assuming all images are available digitally (analog would require conversion) and of sufficiently high quality, it is still possible that the basic image features will not necessarily be standard (e.g. size, resolution, contrast). Our prior experience has been that it is difficult to standardize the CT acquisition protocols, since many of these patients arrive in the emergency
room at odd hours. Fortunately, our analysis methods have so far proven to be robust and insensitive to CT scan variability. An additional concern is the need to properly de-identify DICOM image files, since they have patient identification information embedded as metadata. Lastly, managing the transfer of very large files of any type could be problematic if connectivity is of low quality or interrupted.

METRC is leveraging its existing resources to build a functional image transfer system and avoid the challenges specified above by doing the following. The METRC team will start by working with a handful of sites to identify hurdles to successful implementation, prior to moving forward at all study sites. As part of the study certification process, we will work with each institution to identify the process to be used for gathering, de-identifying, and transferring of image data as well as a key medical imaging contact at the facility. The image transfer procedures will involve burning to CD and mailing to the central reading site.

Further, information about the technology used by the institutions will be gathered to assess the variability in their imaging systems. Patient identifiable information will be removed from the image files. As part of this project, the analysis of the image data will occur at a single site (University of Iowa), which obviates the need to build a more complex infrastructure to analyze the data centrally through a METRC portal.

### 7.2 Laboratory Evaluations

As standard of care during the hospitalization surrounding the surgery, routine laboratory evaluations will be conducted allowing assessment renal function prior to enrolling patients in the study, and of the potential AEs of thrombocytopenia and renal function after the patients begin study medication dosing. Additional labs will not be conducted as part of the study procedures.

### 7.3 Assessment of Participant Adherence with Study Treatment

Patient will use the space provided on the medication blister pack packaging (see section 7.1.2 above) will be used to assess medication adherence and any complications or side effects experienced while not in the hospital. Participants will also be asked to bring back the empty blister packs to serve as a surrogate assessment of patient compliance with the protocol.

### 7.4 Billing Data

Patients will be asked to provide access to billing data in the form of hospital charges at the revenue center/cost department (UB92 hospital bills) from the index hospital and any other rehospitalization during the year following the injury. Costs will be calculated from charges at the revenue center/cost department line level using cost-to-charge ratios (CCRs) computed from the Medicare Cost Reports (MCRs) specific to the hospital and fiscal year of the hospital stay. We will also collect self reported utilization data on number of outpatient visits for medical care as well as indirect costs associated with informal caregiver time spent taking care of the
participant. These data will be used to estimate total costs associated with care in both treatment groups.

8. STUDY SCHEDULE

8.1 Screening

Study coordinators will identify potentially eligible patients for the Pain study through daily monitoring of the orthopedic trauma census. Study coordinators will assess patients for study eligibility at one of the following points of enrollment: admission to the study hospital for acute care of their injury; transfer to the study hospital after a stay of less than 24 hours at the transferring facility; or; pre-fixation assessment visit after discharge from the study hospital emergency department.. Screening and enrollment will occur within 48 hours of admission to the study hospital or at the first pre-fixation assessment visit. The assessment will include a review of the medical record to ensure none of the study exclusion criteria are met. The study will be discussed with potentially eligible patients.

8.2 Enrollment/Baseline

After eligibility is confirmed by the Site Investigator, patients will be approached for their consent to participate in the randomized controlled trial. Informed consent will be obtained prior to initiation of study medications, but will not impede standard of care pain management. Often, patients are initially provided with temporary external fixation or splinting to allow for swelling to decrease prior to definitive fixation (typically 7-14 days following the injury). Enrollment will be conducted within 10 days of injury. Patients enrolled in the inpatient environment will be consented and randomized within the first 48 hours after admission to the study hospital, start on a study medication arm, and will likely be discharged home with the medication if they have not yet had definitive fixation. If a patient is treated and discharged from the emergency department and then presents for an orthopaedic consultation prior to definitive fixation, the patient may also be assessed for eligibility and enrolled during the pre-fixation assessment visit.

The attending surgeon will be involved in the consent conversation. The conversation will be initiated by the research coordinator and surgeon together. The consent process will involve a dialogue. Specifically, patients and their families will be provided with a pamphlet describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate (Attachment I). This conversation will include discussion of the PTOA pilot study, and allow patients to check a box on the consent form (Attachment F) allowing the research team to contact them following definitive fixation to obtain an additional CT scan. Patients will also view a video (Script Attachment J) which will provide further information about study participation. Prior to obtaining consent, the patient’s ability to provide informed consent will be assessed using Attachment H, the Evaluation to Give Consent. Following definitive fixation, up to 60 patients with pilon fractures who did not receive a post-operative CT scan will be contacted by the study team, and written informed consent to participate in the PTOA pilot study will be obtained.
All consent must be obtained from the patient in this study; no legally authorized representatives or surrogates may consent on behalf of the patient. This is due to the subjective nature of assessing pain. All recruitment materials will be provided in both English and Spanish.

Once consented into the Pain study, baseline data regarding patient characteristics, injury characteristics, fracture classification and medical history and co-morbidities, including current use of pain medication, will be collected and entered into the REDCap data collection system. Some of this information will be obtained via a brief interview with the patient (See Attachment C for details).

8.3 Randomization

Once the eligibility of the patient for study inclusion has been determined and the patient has been consented with assistance from the treating surgeon, the Research Coordinator will update the REDCap Data Management System and the patient will be randomized electronically to a Pain study treatment arm. To ensure that the number of subjects is about the same in the three arms of the study for each clinical site, the randomization scheme will assign patients in a 1:1:1 ratio in randomly permuted blocks of assignments stratified by clinical center. Block size will be determined randomly and the patient will be the unit of randomization. Recruitment into the PTOA pilot study will be independent of randomization block and be based solely on the type of injury and the lack of standard of care post-operative CT scan following definitive fixation.

The Research Coordinator will communicate the results of the randomization (group number) to the treating physician and the research pharmacy along with the exact date and time of the randomization. Enrollment and randomization results will be documented in the patient’s chart according to center protocol.

8.4 Follow-up

Data will be prospectively collected largely using the normal clinical course of follow-up. Initial demographic and injury data will be collected during the initial hospital admission. Follow-up data will be collected at 3, 6 and 12 months (plus or minus two weeks) following injury, which follow standard of care. At these visits, data will be collected related to pain and well being, as outlined in Appendix C. Additionally, patients will be asked about any rehospitalizations and billing data will be collected from those visits. Patients with complications will likely be seen more frequently than this, and the patient will be assessed by the research coordinator to determine if the visit is related to an adverse event related to the study procedures. In these cases, the event will be reported according to the protocol (Section 9). Follow-up will be arranged prior to discharge and will be monitored closely by research personnel, who will contact patients who miss follow-ups and assist in scheduling to minimize study losses to follow-up. The study coordinator at each site will be trained to engage the patient prior to discharge and help motivate them to comply with follow-up assessments (see Section 8.4.1: Retention). Our sample size calculations assume 10% loss to follow-up. If patients are routinely followed beyond 12 months, any images collected as part of clinical care at those visits, up to 24 months following definitive fixation, will be obtained. The 60 patients consented to the PTOA pilot
study will be actively followed for up to an additional 12 months for assessment of final PTOA status at 24 months following definitive fixation.

8.4.1 Retention

The study participants will receive an honorarium in recognition of their time and effort. Patients who participate only in the main Pain study will be compensated as follows: a $25 payment for returning the medication blister pack; a $25 payment will be given for completing each of the first 2 follow-up visits at 3 and 6; $50 will be given at the final, 12 month follow-up. (a total of $125 per patient for returning packaging and completing all 3 follow-ups). The 60 patients participating in the additional PTOA pilot study will receive an additional $25 for the both the CT scan up to 3 months following fixation and the final radiographic study at 24 months. We will also keep participants engaged through use of study updates on the METRC website and distribution of follow-up reminders.

8.5 Final Study Visit

The majority of patients will complete their final study visit at 12 months following injury. At this visit, a final interview will be conducted and standard of care radiographic images will be taken. For patients with a pilon fracture consented into the PTOA pilot study, the final study visit will occur at 24 months following definitive fixation, at which point the patient will provide data to complete an AOS assessment and undergo a final set of radiography images.

If a participant is unable to return to the clinic for a final follow-up visit, or for any interim visit, the patient reported outcomes by be obtained by telephone and the participant will receive payment for the visit.

8.6 Early Termination Visit

If a patient decides to terminate participation, or if a surgeon removes a patient from the study, every attempt will be made to complete a final interview to obtain outcome-related data.

8.7 Pregnancy Visit

Participants who become pregnant during the study will be asked to continue participating in study follow up interviews. Because radiographic follow up in this study adheres to standard of care, follow up radiographs would only be obtained if considered clinically appropriate and safe by their treating surgeon. Pregnant patients would not be considered eligible for the PTOA pilot study.

8.8 Unscheduled Visits

Patients with complications will likely be seen more frequently than this, and the patient will be assessed by the research coordinator to determine if the visit is related to an adverse event related to the study procedures. In these cases, the event will be reported according to the protocol (Section 9).
9. ASSESSMENT OF SAFETY

The study will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the “Common Rule”, shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of “unanticipated problems” involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head.

The medical monitor (MM) is responsible for providing medical guidance and overseeing patient safety for the study. The MM participates in determining the course of action necessary to meet safety goals and objectives. This is achieved through the review of Serious Adverse Event reports; resolving safety issues; and interacting with Principal Investigators.

Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

9.1 Definitions

9.1.1 Adverse event

Any untoward or unfavorable medical occurrence in a human subject, including abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom or disease temporally associated with the subject’s participation in the study, whether or not considered related to the subject’s participation.

9.1.2 Unanticipated problem

Any incident, experience, or outcome that meets all of the following criteria:

(1) is unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol and informed consent document and the characteristics of the patients eligible for the study.

(2) is related or possibly related to treatment/procedures under study; possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the study procedures or treatments.

(3) suggests that the participation in the study may place subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Please note that not all adverse events are unanticipated problems and only some unanticipated problems are in fact adverse events. For instance, if a laptop containing study data is stolen, this is an unanticipated problem but it is not an adverse event since it is not an untoward or unfavorable medical occurrence in a human subject.
9.1.3 Serious Adverse Event

A serious adverse event is defined as:

1. Death
2. Unanticipated events related to use of any of the study medications.
3. Other events that are unexpected AND serious AND related or possibly related to the study

9.2 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

9.2.1 Methods and Timing of Assessment

Adverse events and complications will be assessed daily during the inpatient phase of the study and at the three, six, and twelve month follow-up visits, as well as during any unscheduled visit to a clinic. The events will be recorded on study data forms, with a determination of whether or not they are thought to be associated with the study or with one of the study treatments. Additionally, patients will record adverse events and complications in their daily log through the time of their rehospitalization for definitive fixation. In this study, adverse events will be monitored as secondary outcomes of the study (e.g. non-union, infection, somnolence, dizziness, headaches, and other central nervous system effects, peripheral edema, visual changes, and dry mouth, excessive bleeding, gastrointestinal bleeding, deep vein thrombosis, and thrombocytopenia). The adverse events we are monitoring are expected in the type of patients receiving the medications administered in this study (Appendix E: Common and Infrequent Side Effect for Study Drugs).

9.2.2 AE/SAE Grading and Relationship Assignment

Adverse event grading: Adverse events will be graded according to the table provided in Appendix D. Relationship between AE and test article will be made by the site Investigator(s).

9.2.2.1 Adverse Events related to meloxicam, ketorolac and pregabalin

The study will capture safety information on meloxicam, ketorolac and pregabalin, the drugs used in this study. Potential adverse drug effects, side effects and laboratory monitoring for the drugs utilized in this study are outlined in Appendix E.

9.2.3 Recording and Documentation

Sites will maintain source documents including but not limited to laboratory and radiology reports, clinical notes and discharge summaries. After review of initial and final reports by the medical monitor, the events may be reclassified at their discretion.

9.2.4. Management of Adverse Events
Adverse Events and Serious Adverse Events will be managed according to protocol guidelines. If specific guidelines do not exist, AEs/SAEs will be managed according to the medical judgment of the treating physician.

9.3 Adverse Event Reporting Procedures

9.3.1 Non-Reportable Adverse Events

Adverse events collected as study outcomes such as non-union, infection, somnolence, dizziness, headaches, and other central nervous system effects, peripheral edema, visual changes, dry mouth, excessive bleeding and thrombocytopenia will be recorded on study data forms whether or not they are thought to be associated with the study or with one of the treatments. These events do not need to be reported to the MCC as adverse events because they are reported via study forms.

9.3.2 Local Reporting Requirements.

Study sites must always follow and comply with their own local institution’s adverse event reporting requirements, which may differ from those adopted by the Pain/PTOA study. Depending on the local requirements, a site may report events locally and not report those events to the METRC Coordinating Center. Each participating site is responsible for ensuring that all local IRB requirements for reporting adverse events (both internal and external) are met.

9.3.3 SAE and Unanticipated Problem Reporting Requirements

All Serious Adverse Events must be reported to the METRC Coordinating Center with 72 hours.

In addition, unanticipated problems that are not adverse events must also be reported to the METRC Coordinating Center according to the procedures outlined in the METRC Manual of Operations as soon as possible after the event.

The medical monitor for this study is:

Marc Swiontkowski, MD
Professor of Orthopaedic Surgery
University of Minnesota
2512 South 7th Street
Suite R200
Minneapolis, MN 55454
Phone: (612) 273-8000
Email: swion001@umn.edu

SAEs will be reported to METRC to the attention of:

Renan Castillo, PhD, Principal Investigator
All SAEs related to use of study medications will be reported to the individual manufacturers to contribute safety data for these drugs, as well as to the FDA via the MedWatch voluntary reporting mechanism using form FDA 3500.

### 9.3.4 METRC Coordinating Center Reporting Responsibilities

The MCC will send a copy of each report received about a serious adverse event judged reportable to all clinical sites, with instructions for each to forward the report to their IRB.

Copies of the report will also be sent to the DoD, the Study PI, and to the Medical Monitor. The MCC will maintain a list of such events for reporting and review at Steering Committee meetings.

### 9.3.5 Department of Defense Reporting Requirements

The following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command’s (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO).

1. The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.
2. Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.
3. All unanticipated problems involving risk to subjects or others must be promptly reported by phone (301-619-2165), by email (HRPO@amedd.army.mil or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.
4. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.
(5) Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.

(6) Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implication (e.g. adding children, adding active duty population, etc.), significant changes in study design (i.e. would prompt a scientific review) or a change that could potentially increase risk to subjects. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.

(7) A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.

(8) The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

9.4 Reporting Pregnancy

Pregnancy is an exclusion criterion for participation in the Pain study and the PTOA pilot study. However, if a woman becomes pregnant during the follow-up period, it will not affect her ability to participate in the study as no further medications will be administered. She will receive standard of care imaging studies as directed by her physician. A woman who is pregnant at the time of consent for the PTOA pilot study will remain ineligible. No additional reporting requirements are necessary, as pregnant women will not be placed at increased risk as participants in this study.

9.5 Type and Duration of the Follow-up of Participants After Adverse Events

Study patients who experience a SAE will be followed until resolution of the event, and a final report will be submitted to the medical monitor, the coordinating center and the pharmaceutical company (if applicable).

9.6 Modifications of Study Agent(s)/Intervention(s) for a Participant

Two of the study medications are either excreted renally (pregabalin) or affect renal function (ketorolac). Therefore, doses will be reduced for patients age 65 and greater, inclusive, in addition to those with moderate renal impairment and those with severe or overt renal failure will excluded. Glomerular Filtration Rate (GFR) will be calculated using the most conservative of
the MDRD Study (Modification of Diet in Renal Disease Study) equation,\textsuperscript{75} or the CKD EPI (Chronic Kidney Disease Epidemiology Collaboration) calculation.\textsuperscript{76} This calculation will be normalized to patients body surface area using the formula recommended by Mosteller.\textsuperscript{77} (BSA (m\textsuperscript{2}) = \text{Sqrt}[\text{Height (cm)} \times \text{Weight(kg)}/3600]). These calculations will be performed by REDCap using height, weight, creatinine level, age, gender, and race. Normal renal function will be defined as having a GFR greater than or equal to 60; moderate renal impairment will be defined as a GFR of 30-59, and patients with a GFR of less than 30 will be excluded from the study.

For patients who require a modified dose, the proposed dosing schedule of 30 mg IV ketorolac every 6 hours and 75 mg pregabalin every 12 hours will be halved to 15 mg ketorolac every 6 hours and 75 mg pregabalin daily, so that the patient will only receive $1/2$ the dose dispensed by the pharmacy. Labeling on the package and generated by REDCap inclusion criteria will serve as reminders of the alternate dosing strategy. The proposed oral dose of pregabalin will be halved by removing one of the daily doses in the blister pack prior to providing it to the patients, and to administer the post-operative oral dose only once per day.

9.7 Halting Rules for the Protocol

See section 9.8.

9.8 Stopping Rules for an Individual Participant/Cohort

The DSMB will review the overall progress of the trial in terms of recruitment and data quality and makes a formal recommendation to the DOD at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications or be stopped.

9.9 Premature Withdrawal of a Participant

A participant may be withdrawn from the study without consent if the sponsor decides to end the study. Other reasons for removing a participant without consent may include but are not limited to non-adherence with the protocol and/or therapy, inappropriate behavior towards study personnel, etc. Additionally, if a patient develops a deep vein thrombosis requiring treatment with anticoagulants during the treatment period (i.e. during the time study medications are being taken), the patient will be immediately withdrawn from treatment to ensure no interactions between study drugs and anticoagulants occur. Withdrawal will be noted on study forms and patients will continue to be followed in the study and analyzed within the intent to treat paradigm. The DVT would be recorded and reported as an adverse event.

9.10 Replacement of a Participant Who Discontinues Study Treatment N/A

10. CLINICAL MONITORING STRUCTURE
10.1 Site Monitoring Plan

The METRC Coordinating Center will be responsible for site monitoring consistent with ICH/FDA guidelines. Site monitoring will occur in a manner consistent with METRC standard operating procedures and will include a combination of remote and onsite monitoring activities to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites’ regulatory files to ensure that regulatory requirements are being followed.

The site PI will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the DOD, the Office for Human Research Protections (OHRP), or other regulatory authorities for confirmation of the study data.

10.2 Safety Monitoring Plan

10.2.1 Safety Review Plan by the DSMB

An independent Data and Safety Monitoring Board (DSMB), appointed by DOD, is responsible for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy, evaluate recruitment, and assess overall data quality. An interim analysis will occur after 50% patients are at 12 months from enrollment.

The DSMB is a multidisciplinary group with a written charge provided by METRC and DOD. The DSMB will meet in person to review the protocol. After the trial commences, the DSMB meets twice a year to review data or other issues. The DSMB may request more frequent meetings if necessary to fulfill it charge. It may also request additional safety reports on a more frequent basis. For example, all serious adverse events (SAE) are reported to the DSMB for their consideration and recommendations as they occur.

At its first meeting the DSMB will review definition of all outcomes, adverse events and serious adverse events and revisions to the protocol made as appropriate. Summary data on adverse events (together with study outcomes) will be monitored by the DSMB at its semiannual meetings or more frequently, as needed. These summaries will include analyses comparing rates of adverse events by blinded treatment group, by clinic, or in other subgroups requested by the DSMB.

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events, for transmission to the IRBs at each of the study centers. Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met.
The DSMB will review semi-annual reports by masked treatment groups of the primary and secondary outcomes as well as all adverse events that are not identified as outcomes per se.

Interim data on safety measures requested by the DSMB are reviewed at each of the scheduled semi-annual full meetings. Analyses will be prepared comparing rates of adverse events by treatment group, by clinical center or by other subgroups as requested by the DSMB. Serious adverse events will be reviewed by the DSMB as they occur with the option of a teleconference if any DSMB member requests.

11. STATISTICAL CONSIDERATIONS

11.1 Overview and Study Objectives

The objective of this study is to definitively resolve questions regarding the use of multimodal pharmacologic pain management for orthopedic trauma patients in the context of a multicenter, randomized clinical trial. The study will test whether adjunctive analgesic therapy during the pre and peri-operative period, in addition to standard of care pain management, can improve overall pain control and pain related outcomes without increasing analgesic related side effects.

In addition, a significant proportion of this population develops chronic PTOA. A sub-objective of this study is to examine the etiology and incidence of chronic pain and PTOA in this population.

11.2 Sample Size Considerations

While the overall sample sizes required to observe the expected differences in pain intensity and morphine equivalent opioid utilization (and other proposed secondary outcome measures) are modest, large sample sizes will be required to detect differences in surgery for nonunions. Our study is powered to establish non-inferiority of the 2 active arms to the control arm with respect to the proportion of nonunions between 6 and 12 months post-surgery. The table below shows the expected distribution of study participants enrolled, by fracture type, based on existing METRC registry data and nonunion rates from the literature and expert opinion from our protocol committee.

<table>
<thead>
<tr>
<th>Injury Type:</th>
<th>One year incidence across participating sites:</th>
<th>Expected Nonunion Rate (%):</th>
<th>Expected Percent Contribution to Study Sample (%):</th>
<th>Expected Nonunions per 100 patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed or Open Calcaneus(I/II)</td>
<td>324</td>
<td>2</td>
<td>5</td>
<td>0.10</td>
</tr>
<tr>
<td>Closed or Open Pilon(I/II)</td>
<td>796</td>
<td>10</td>
<td>12</td>
<td>1.20</td>
</tr>
<tr>
<td>Closed or Open Talus(I/II)</td>
<td>146</td>
<td>8</td>
<td>2</td>
<td>0.16</td>
</tr>
<tr>
<td>Lisfranc</td>
<td>494</td>
<td>8</td>
<td>8</td>
<td>0.64</td>
</tr>
<tr>
<td>Severe Ankle Fracture Dislocation</td>
<td>863</td>
<td>4</td>
<td>13</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Thus, the control proportion of nonunions is expected to be approximately 7%. We utilize a non-inferiority margin of 10%, so that a non-union proportion within an active arm of less than 17% would be considered tolerable given the added benefits provided by the active treatment.

For each of the analyses, we will accept equivalence if the upper limit of a one-sided confidence interval for the difference between the active and control proportions of non-union is less than 10%. To account for inflation of Type I error due to the fact that two active treatment groups are being compared to a common control group, the Dunnett procedure for selecting the limits of the confidence intervals will be used. The limits are selected so that if the true difference is greater than or equal to 10% for one or both of the treatment comparisons, the chance of falsely claiming equivalence will be less than 5%. With a sample size of 165 per treatment arm, there is a 90% chance of accepting equivalence for a given treatment comparison if there is truly no difference for that comparison. If there is truly no difference for both comparisons, there is an 81% chance of accepting equivalence for both the comparisons. To account for missing outcome data (10%), we increase the sample size to 165 per arm. Thus, we will need to recruit a total of 495 participants into this study.

To evaluate the predictive ability of injury severity for PTOA at 12 months, we will estimate the area under the receiver operating characteristics (ROC) curve. The area under the ROC represents the probability that a randomly selected patient with PTOA by 12-24 months will have a higher injury severity score than a randomly selected patient without PTOA by 12-24 months. We expect that the true area under the ROC will be greater than 80%. Further, we expect that 40% of patients with ankle fractures will have PTOA by 18 months. Under these assumptions, a sample size of at least 100 patients (based on the fact that the increased number of injuries allowed in the study as of the 12/22/14 amendment will reduce the proportion of ankle fractures in the study sample) would generate a 95% confidence interval for the area under the ROC curve whose width is less than 20% (e.g., 85% ± 9%). Between the 60 patients actively consented into the PTOA pilot study and the patients with ankle fractures who will routinely be followed for more than 12 months, our combined sample size is expected to be close to 150 patients. However, we are concerned about the sample being biased due to the likelihood that patients who are followed beyond 12 months as part of routine care will likely be more severe than patients who are only followed to 12 months. The 60 pilot study patients with complete CT scans at up to 3 months following fixation and radiographic data to 24 months are not being recruited based on fracture severity and are thus are expected to provide balance on this issue. The sample size of 60 patients is being driven by budgetary constraints.
11.3 Randomization

Once the eligibility of the patient for study inclusion has been determined and the patient has been consented with assistance from the treating surgeon, the Research Coordinator will update the REDCap Data Management System and the patient will be randomized to a Pain study treatment arm electronically. To ensure that the number of subjects is about the same in the three arms of the study for each clinical site, the randomization scheme will assign patients in a 1:1:1 ratio in randomly permuted blocks of assignments stratified by clinical center. Block size will be determined randomly and the patient will be the unit of randomization. There is no randomization in the PTOA pilot study.

11.4 Missing Data

Missing data is a serious concern that complicates the interpretation of the study results. We will address this issue from both a study conduct and analysis perspective. Regarding study conduct, we will:

1. Limit participant burden and inconvenience in data collection
2. Select high quality investigators
3. Provide pre-study training of investigators as well as on-study reinforcement
4. Reimburse investigators based on follow-ups completed not on per-patient basis.
5. Monitor and report missing data rates during the study
6. Emphasize the importance of full participation in the study during the consent process.
7. Collect information on the reasons for missing data.
8. Actively engage participants and educate them about the importance of participation
9. Hold regular Protocol Committee meetings to discuss strategies for follow-up
10. Set targets for acceptable rates of missing data and terminate sites not meeting targets.

While these efforts will help to minimize missing data, we recognize that missing data is inevitable. With this in mind, we will conduct sensitivity analyses to evaluate the robustness of the study results to various untestable assumptions about the missing data mechanism. In addition to unadjusted analyses, which rely on the missing completely at random assumption (testable), we will also estimate treatment effects (utilizing relevant auxiliary information) under the missing at random assumption. Further, we will explore the effect of departures from the missing at random assumption using pattern-mixture and selection modeling techniques.

11.5 Planned Interim Analysis

An independent Data and Safety Monitoring Board (DSMB) will monitor interim data as the trial progresses to ensure patient safety, review efficacy, evaluate recruitment, and assess overall data quality. The DSMB will meet every 6 months. The DSMB may request more frequent meetings if necessary to fulfill its charge. After each meeting, the DSMB will make a formal recommendation as to whether the trial should continue unmodified, continue with protocol modifications, or to be stopped.
11.6 Analysis Plan

Patients will be followed for 1 year post-surgery. Statistical analyses will follow the intent-to-treat paradigm, which means all patients will be analyzed according to the treatment group to which they were randomized. For both binary and continuous outcomes, regression modeling may be employed if concerns about confounding arise due to imbalances between treatment groups. Random effects regression modeling may also be used if concerns emerge about the clustering of outcomes within surgeons or centers.

**Binary Endpoints.** Treatment effects for binary endpoints (e.g., adverse effects, complications) will be estimated using a two-group binomial comparison of proportions; confidence intervals for the absolute risk difference and relative risk will be reported. Tests of the null hypothesis of no treatment effect will be based on both a Chi-squared test and a Fisher’s exact test – p-values will be reported.

**Continuous Endpoints.** Treatment effects for continuous endpoints (e.g., SFMA, pain intensity) will be estimated using a two-group comparison of means; confidence intervals for the difference in means will be reported. Tests on the null hypothesis of no treatment effect will be based on both a t-test and a Wilcoxon rank-sum test and p-values will be reported.

**Medical Costs.** The standard economic evaluation approach to assessing the difference between alternative interventions is to construct incremental cost-effectiveness ratios in which the numerator is the difference in healthcare costs for perioperative care versus standard-care patients and the denominator is the between-group difference in the outcome measure of interest. Our expectation is that outcomes will be superior and costs will be lower with the use of perioperative pain management. In this case (which reflects cost-savings even if the clinical outcomes are not significantly different), the incremental cost-effectiveness ratio is not relevant. Both the estimated outcome and cost differences will have variation, however, and accounting for uncertainty in estimates has become an important component of economic evaluation. We will use techniques that consider the joint density of cost and effect differences, together with cumulative density plots known as cost-effectiveness acceptability curves (CEAs) to summarize the interventions’ effects and costs.

**Missing Data.** As with most prospective studies, missing data will be unavoidable (even with excellent follow-up). Since the informative nature of missing data cannot be verified from the observed data, we will adopt a sensitivity analysis framework for reporting results. We will analyze data under a variety of modeling assumptions regarding how strongly the missingness mechanism is related to outcomes.

**PTOA Analysis plan.** To evaluate whether contact stress is an independent predictor of PTOA at 24 months above and beyond, we will fit a logistic regression model with PTOA at 18 months as the dependent variable and injury severity and contact stress as independent variables. We will test whether the coefficient for contact stress is different than zero at the 0.05 type-I error level. For power calculation purposes, we made the following assumptions: (1) the correlation between injury severity and contact stress is 0.5 and (2) the incidence of PTOA by 24 months at the mean
value of contact stress is 20%. We estimate that we will be able to collect complete data on over 150 patients as part of the observational PTOA pilot study. However, if we were able to collect data on only 75 patients (the 60 purposefully sampled and any other patients followed up to 24 months according to standard of care), this sample would provide 80% power to detect an odds ratio of 2.54 (i.e., the study will be, at a minimum, powered to detect an 2.54 increase in the odds of PTOA per unit change in contact stress, after adjusting injury severity).51

We will also analyze PTOA as a time to event variable, using proportional hazard regression models. Analyses of the ordinal KL outcome will use proportional odds regression models and analyses of secondary outcome measures, such as MFA, AOS, SF-36, will be based on generalized linear regression models.74

12. QUALITY CONTROL AND QUALITY ASSURANCE

Compliance regarding the proper treatment protocols will be monitored by local research coordinators in cooperation with the attending surgeons. Any deviation from the assigned treatment group and the actual treatment received will be recorded.

Quality Control (Q/C) and Quality Assurance (Q/A) procedures that apply to all studies are outlined in the METRC Manual of Operations (MOP). A certification process (also outlined in the MOP) will be used as a basis for training and certification of the study personnel involved in data collection. In addition to consortium wide training and certification procedures, additional requirements may be added based on the nature of the study. Ongoing data edits and audits will be performed to ensure collection of quality data. The continuous and timely flow of data from the centers to the MCC is an essential prerequisite for maintaining data quality.

Monthly Performance Reports will be distributed to each center summarizing among other things: recruitment, randomization, status of follow-up, data completion, and timelines of data entry.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 IRB/Ethics Committee

IRB approval will be obtained from the MCC at Johns Hopkins Bloomberg School of Public Health, the DoD, and each participating clinical site according to METRC policies and procedures. Sites that recruit patients will submit their recruitment materials to their IRB prior to use.

Sites must provide the Coordinating Center with a copy of the initial IRB approval notice and subsequent renewals as well as copies of the IRB approved consent statements.
No site can begin work related to this study until the site has been certified in accordance with METRC policies and procedures.

**13.2 Informed Consent Process**

**13.2.1 Consent and Enrollment**

A prototype consent has been prepared for the PAIN/PTOA study and is attached in Appendix F & G. Individual sites may add material but may not delete material thought to be necessary for informed consent. Clinical sites may reformat and reword information to conform to their local requirements. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the signed consent forms will be given to the patient, and this fact will be documented in the patient’s record.

Eligible patients will be approached for their consent to participate. Informed consent will be obtained prior to definitive wound closure or coverage.

The attending surgeon will be involved in the consent conversation. The conversation will be initiated by the research coordinator and surgeon together. Patients will be informed of the study goals and data to be collected. A video describing the study will be shown (Appendix J). Additionally, Patients and their families will be provided with a pamphlet (Appendix I) describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate.

All written recruitment materials will be provided in both English and Spanish.

**13.2.2 Assessing Capacity to Consent and Consenting a Proxy Respondent**

Due to the subjective nature of assessing pain, in this study, no proxy consent will be obtained. Prior to initiating the consent process, the Research Coordinator will contact the participant’s treating physician for confirmation that the participant has the ability to understand the relevant study information and communicate and maintain a choice. If the physician indicates that the patient lacks the capacity to consent, the patient will be declared ineligible.

The research staff will endeavor to answer all questions posed by the patient and his/her family to ensure their understanding of the protocol. A limited number of questions will be asked of all patients after they are introduced to the study and have reviewed the consent form. These questions assess the person’s understanding of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation. A formal comprehension test may be utilized, or comprehension will be assessed by the person(s) obtaining the consent. A template for a comprehension test is provided in Appendix G.

The Research Coordinator will ask the questions and determine the appropriateness of the responses. If the Research Coordinator is at all unsure about the patient’s ability to consent s/he will consult with the study site PI.
13.3 Exclusion of Women, Minorities, and Children (Special Populations)

The proposed study anticipates recruiting a significant proportion of racial/ethnic minorities (African-Americans, Asian-Americans and Hispanics) as well as non-Hispanic white subjects. The study will not include children or prisoners.

13.4 Participant Confidentiality

It is the investigator’s responsibility to conduct the protocol under the current version of Declaration of Helsinki, ICH Guidelines, Good Clinical Practice, and rules of local IRBs. The investigator must ensure that the patient’s anonymity be maintained in their data submission to the Data Coordinating Center.

Patients will be identified only by an identification code but not by their name, SSN, or hospital medical record number. Study Site Investigators will maintain a separate confidential enrollment log which matches identifying codes with the patients’ names and addresses (i.e., available only to local clinic staff).

All study forms, reports, and other records that are part of the study data collection materials will be identified by coded number to maintain patient confidentiality. All paper, records will be kept in locked file cabinets. All electronic records of study data will be identified by coded number. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the IRB, DOD, or DSMB. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB and DOD requirements for compliance with The Health Insurance Portability and Accountability Act (HIPPA).

13.5 Study Discontinuation

Participants will be informed that they may discontinue the study at any time, for any reason. They will be assured that the medical care which they receive at the participating facility will not be affected should they elect to discontinue participation in the study.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management Responsibilities

Instructions concerning the recording of study data on case report forms will be provided by the METRC Coordinating Center. Each study site is responsible for transmitting the data in a timely fashion.

The research coordinators at each site will obtain the information necessary to complete the case report forms (CRFs) from several sources including but not limited to, the patient’s medical record, clinical evaluations and patient interviews. These forms will NOT contain the patient’s
name, SSN, or hospital medical record number; they will be identified only by a unique patient-
specific study number.

The Site Research Coordinator will enter non-personally identifiable information into a central
and secured web-based data management system being implemented for all Consortium studies,
known as REDCap. This data management system has incorporated state-of-the-art features for
electronic data collection and is configured in accordance with best practices for information
technology and research data management.

Hard copy documents containing subject data and patient identifiers (and contact information)
will be stored in secure document containers (file cabinets, lockers, drawers, etc.) in accordance
with standard document management practices. The data collection forms will be destroyed
within five years after study completion, as will the file linking study numbers with personally
identifiable information. Paper forms will be shredded and the file containing personally
identifiable data at each site will be deleted from local site computers. Each site will provide the
Coordinating Center a signed verification that these data have been destroyed.

All research data, in hard copy or electronic form, will be stored and managed in a secure
manner following applicable federal regulations and guidelines and according to institutional
policies and practices.

At all times only listed key personnel specifically designated and authorized by the Principal
Investigator shall have access to any research related documents, including electronic data. All
such personnel will be properly trained and supervised regarding the management and handling
of confidential materials. The Principal Investigator assumes full responsibility for such training,
supervision, and conduct.

Research related documents (including electronic data), and medical records will be accessible
only by key personnel specifically designated and authorized by the Principal Investigator. All
such personnel will be properly trained and supervised regarding the management and handling
of confidential materials. The Principal Investigator assumes full responsibility for such training,
supervision, and conduct. This information will also be available for audit by study monitors and
representatives of the local IRB, the MCC, the DOD (and other study sponsors if applicable), the
FDA and the OHRP.

14.2 Data Capture Methods

Data will be collected in real time by the investigator or study coordinator directly on paper Case
Report Forms (CRFs) which will serve as source documents for the study. Source documents
will be signed by PI, other site Investigator, or Research Coordinator including both the CRFs
and other medical records (e.g. laboratory & radiology reports, clinical notes and discharge
summaries. The Research Coordinator, or an MCC-certified staff member working under the
supervision of the research coordinator, will enter the data from the CRFs into the REDCAP
database.
14.3 Types of Data

Data will include medical and surgical histories, laboratory reports, radiologic studies, adverse events and patient interviews

14.4 Source Documents and Access to Source Data/Documents

Source documents including CRFs, laboratory results, patient surveys, medical records, etc. will be maintained at the site and will be made available to study monitors, and representatives of regulatory agencies including the study sponsor (MCC), IRB, FDA and OHRP.

14.5 Timing/Reports

The MCC will send site queries on a weekly basis and site progress reports monthly.

14.6 Study Records Retention

Study records will be maintained in accordance with current ICH guidelines.

14.7 Protocol Deviations

Records of protocol deviations will be noted on the appropriate METRC form with the reason for the deviation recorded, as well as any action taken to mitigate the deviation. These records will be provided to the site’s IRB in accordance with local reporting requirements and be made available to study monitors.

15. PUBLICATIONS POLICY

Publications will be written in accordance with the METRC publication policy (available on the METRC website: www.metrc.org).

16. SCIENTIFIC REFERENCES


41. Field r J.et al Pharmacol 1997;121:1513-22


17. APPENDICES APPENDIX A: STUDY CONTACT ROSTER

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APPENDIX B: PROTOCOL COMMITTEE

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Vanderbilt Medical Center

Tara Taylor, MPH  
Johns Hopkins Bloomberg School of Public Health

Study website: www.metrc.org
# APPENDIX C: DATA COLLECTION SCHEDULE

<table>
<thead>
<tr>
<th>Assessment/Procedure</th>
<th>Respondent</th>
<th>Baseline</th>
<th>48 hrs. post def. fix</th>
<th>3 month</th>
<th>6 month</th>
<th>12 month</th>
<th>24 month</th>
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<tr>
<td>Informed Consent</td>
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<td>Inclusion/Exclusion criteria</td>
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<td>Multidimensional Post Surgical Pain Scale*</td>
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<td>X</td>
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<td>Randomization</td>
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<td>Patient Information/Contact</td>
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<td>Patient Demographics</td>
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<td>Injury Characteristics and Treatments</td>
<td>Medical Record</td>
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<td>From enrolment to 48 hrs post fixation</td>
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<td>Daily Assessment of Pain Scores and Side Effects</td>
<td>Patient, Blister-pack packaging</td>
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<td>Pain Intensity Visual Analog Scale</td>
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<td>Concomitant Medications</td>
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<td>Complications (see Appendix E for list)</td>
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<td>Laboratory Results</td>
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<td>Rehospitalization Form</td>
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<td>Pain Protocol v 9.0 12/22/2014</td>
<td>Medical Record/Surgeon</td>
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<td>Study Surgery (OR Trip) Form</td>
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<td>Clinic Follow-up/Interim Visit Form</td>
<td>Surgeon</td>
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<td>(ongoing)</td>
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<tr>
<td>Brief Pain Inventory* + painDETECT *</td>
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<td>VR-12*</td>
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<td>Short Musculoskeletal Function Assessment*</td>
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<td>PTSD Check List (PCL)*</td>
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<td>Patient Health Questionnaire – 9 (Depression)</td>
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<tr>
<td>Ankle Osteoarthritis Scale (AOS)*</td>
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<td>X</td>
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<td>Radiographs</td>
<td>Per SOC: Before &amp; after each surgery + 3, 6,12, and 24 (subset of patients) months</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Adverse Events Log (ongoing form)</td>
<td>Research Coordinator/Surgeon</td>
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</tr>
<tr>
<td>Medical History Log (ongoing form)</td>
<td>Research Coordinator/Surgeon</td>
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<tr>
<td>SAE (as needed)</td>
<td>Research Coordinator/Surgeon</td>
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<tr>
<td>CT Scan Form</td>
<td>Per SOC: Before and after definitive fixation: at 3 months for a subset of patients</td>
<td>X</td>
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<tr>
<td>Medical Costs (UB92 Billing Records)</td>
<td>baseline &amp; interim surgeries and any rehospitalization</td>
<td>X</td>
<td>X</td>
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<tr>
<td>KL Scale Analysis from Radiographs</td>
<td>University of Iowa</td>
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<td></td>
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</tr>
</tbody>
</table>

* Previously validated instrument

1. As clinically indicated
APPENDIX D: ADVERSE EVENT GRADING TABLE*

ABBREVIATIONS: Abbreviations utilized in the Table:
ULN = Upper Limit of Normal   LLN = Lower Limit of Normal
Rx = Therapy                   Req = Required
Mod = Moderate                 IV = Intravenous
ADL = Activities of Daily Living   Dec = Decreased

ESTIMATING SEVERITY GRADE
For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1 Mild          Transient or mild discomfort                      (< 48 hours); no medical intervention/therapy required
GRADE 2 Moderate      Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3 Severe        Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4 Life-threatening Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5 DEATH* NOTE: Tables below do not reflect Grade 5 because any resulting death, regardless of grade is a Grade 5.

SERIOUS OR LIFE-THREATENING AEs
ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 event.
Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

DURATION TOXICITY TABLE
NOVEMBER 2007 ADVERSE EVENT GRADING TABLE

COMMENTS REGARDING THE USE OF THIS TABLE
Standardized and commonly used toxicity tables (Division of AIDS, NCI’s Common Toxicity Criteria (CTC), and World Health Organization (WHO) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
For parameters not included in the following Toxicity Tables, sites should refer to the “Guide For Estimating Severity Grade” located above.
Criteria are generally grouped by body system.
Some protocols may have additional protocol specific grading criteria, which will supercede the use of these tables for specified criteria
### HEMATOLOGY

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>9.5 - 10.5 gm/dL</td>
<td>8.0 - 9.4 gm/dL</td>
<td>6.5 - 7.9 gm/dL</td>
<td>&lt; 6.5 gm/dL</td>
</tr>
<tr>
<td><strong>Absolute Neutrophil Count</strong></td>
<td>1000-1500/mm³</td>
<td>750-999/mm³</td>
<td>500-749/mm³</td>
<td>&lt;500/mm³</td>
</tr>
<tr>
<td><strong>Platelets</strong></td>
<td>75,000-99,999/mm³</td>
<td>50,000-74,999/mm³</td>
<td>20,000-49,999/mm³</td>
<td>&lt;20,000/mm³</td>
</tr>
<tr>
<td><strong>WBCs</strong></td>
<td>11,000-13,000/mm³</td>
<td>13,000-15,000/mm³</td>
<td>15,000-30,000/mm³</td>
<td>&gt;30,000 or &lt;1,000/mm³</td>
</tr>
<tr>
<td><strong>% Polymorphonuclear Leucocytes + Band Cells</strong></td>
<td>&gt; 80%</td>
<td>90 – 95%</td>
<td>&gt;95%</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Abnormal Fibrinogen</strong></td>
<td>Low: 100-200 mg/dL</td>
<td>Low: &lt;100 mg/dL</td>
<td>Low: &lt; 50 mg/dL</td>
<td>Fibrinogen associated with gross bleeding or with disseminated coagulation</td>
</tr>
<tr>
<td></td>
<td>High: 400-600 mg/dL</td>
<td>High: &gt;600 mg/dL</td>
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<td></td>
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<tr>
<td><strong>Fibrin Split Product</strong></td>
<td>20-40 mcg/ml</td>
<td>41-50 mcg/ml</td>
<td>51-60 mcg/ml</td>
<td>&gt; 60 mcg/ml</td>
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<tr>
<td><strong>Prothrombin Time (PT)</strong></td>
<td>1.01 - 1.25 x ULN</td>
<td>1.26-1.5 x ULN</td>
<td>1.51 - 3.0 x ULN</td>
<td>&gt;3 x ULN</td>
</tr>
<tr>
<td><strong>Activated Partial Thromboplastin (APPT)</strong></td>
<td>1.01 -1.66 x ULN</td>
<td>1.67 - 2.33 x ULN</td>
<td>2.34 - 3 x ULN</td>
<td>&gt; 3 x ULN</td>
</tr>
<tr>
<td><strong>Methemoglobin</strong></td>
<td>5.0 - 9.9 %</td>
<td>10.0 - 14.9 %</td>
<td>15.0 - 19.9%</td>
<td>&gt; 20.0 %</td>
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</table>

### ENZYMES

<table>
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<th></th>
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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AST (SGOT)</strong></td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
<tr>
<td><strong>ALT (SGPT)</strong></td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
<tr>
<td><strong>GGT</strong></td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
</tr>
<tr>
<td><strong>Alkaline Phosphatase</strong></td>
<td>1.1 - &lt;2.0 x ULN</td>
<td>2.0 – &lt;3.0 x ULN</td>
<td>3.0 – 8.0 x ULN</td>
<td>&gt; 8 x ULN</td>
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<tr>
<td><strong>Amylase</strong></td>
<td>1.1 - 1.5 x ULN</td>
<td>1.6 - 2.0 x ULN</td>
<td>2.1 - 5.0 x ULN</td>
<td>&gt; 5.1 x ULN</td>
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<tr>
<td><strong>Lipase</strong></td>
<td>1.1 - 1.5 x ULN</td>
<td>1.6 - 2.0 x ULN</td>
<td>2.1 - 5.0 x ULN</td>
<td>&gt; 5.1 x ULN</td>
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<tr>
<td>CHEMISTRIES</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
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<tr>
<td>-------------</td>
<td>---------</td>
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<tr>
<td><strong>Hyponatremia</strong></td>
<td>130-135 mEq/L</td>
<td>123-129 mEq/L</td>
<td>116-122 mEq/L</td>
<td>&lt; 116 mEq/L or abnormal sodium with mental status changes or seizures</td>
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<tr>
<td><strong>Hypernatremia</strong></td>
<td>146-150 mEq/L</td>
<td>151-157 mEq/L</td>
<td>158-165 mEq/L</td>
<td>&gt; 165 mEq/L or abnormal sodium with mental status changes or seizures</td>
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<td><strong>Hypokalemia</strong></td>
<td>3.0 - 3.4 mEq/L</td>
<td>2.5 - 2.9 mEq/L</td>
<td>2.0 - 2.4 mEq/L or intensive replacement therapy or hospitalization required</td>
<td>&lt; 2.0 mEq/L or abnormal potassium with paresis, ileus or life-threatening arrhythmia</td>
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<td><strong>Hyperkalemia</strong></td>
<td>5.6 - 6.0 mEq/L</td>
<td>6.1 - 6.5 mEq/L</td>
<td>6.6 - 7.0 mEq/L</td>
<td>&gt; 7.0 mEq/L or abnormal potassium with life-threatening arrhythmia</td>
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<tr>
<td><strong>Hypoglycemia</strong></td>
<td>55-64 mg/dL</td>
<td>40-54 mg/dL</td>
<td>30-39 mg/dL</td>
<td>&lt;30 mg/dL or abnormal glucose with mental status changes or coma</td>
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<tr>
<td><strong>Hyperglycemia (nonfasting and no prior diabetes)</strong></td>
<td>116 - 160 mg/dL</td>
<td>161 - 250 mg/dL</td>
<td>251 - 500 mg/dL</td>
<td>&gt; 500 mg/dL or abnormal glucose with ketoacidosis or seizures</td>
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<tr>
<td><strong>Hypocalcemia (corrected for albumin)</strong></td>
<td>8.4 - 7.8 mg/dL</td>
<td>7.7 - 7.0 mg/dL</td>
<td>6.9 - 6.1 mg/dL</td>
<td>&lt; 6.1 mg/dL or abnormal calcium with life threatening arrhythmia or tetany</td>
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<td>CHEMISTRIES (continued)</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
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</tr>
<tr>
<td>Hypercalcemia (correct for albumin)</td>
<td>10.6 - 11.5 mg/dL</td>
<td>11.6 - 12.5 mg/dL</td>
<td>12.6 - 13.5 mg/dL</td>
<td>&gt; 13.5 mg/dL or abnormal calcium with life threatening arrhythmia</td>
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<tr>
<td>Hypomagnesemia</td>
<td>1.4 - 1.2 mEq/L</td>
<td>1.1 - 0.9 mEq/L</td>
<td>0.8 - 0.6 mEq/L</td>
<td>&lt; 0.6 mEq/L or abnormal magnesium with life-threatening arrhythmia</td>
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<tr>
<td>Hypophosphatemia</td>
<td>2.0 - 2.4 mg/dL</td>
<td>1.5 - 1.9 mg/dL or replacement Rx required</td>
<td>1.0 - 1.4 mg/dL intensive therapy or hospitalization required</td>
<td>&lt; 1.0 mg/dL or abnormal phosphate with life-threatening arrhythmia</td>
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<td>Hyperbilirubinemia (when accompanied by any increase in other liver function test)</td>
<td>1.1 - &lt;1.25 x ULN</td>
<td>1.25 - &lt;1.5 x ULN</td>
<td>1.5 – 1.75 x ULN</td>
<td>&gt; 1.75 x ULN</td>
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<tr>
<td>Hyperbilirubinemia (when other liver function are in the normal range)</td>
<td>1.1 - &lt;1.5 x ULN</td>
<td>1.5 - &lt;2.0 x ULN</td>
<td>2.0 – 3.0 x ULN</td>
<td>&gt; 3.0 x ULN</td>
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<tr>
<td>BUN</td>
<td>1.25 - 2.5 x ULN</td>
<td>2.6 - 5 x ULN</td>
<td>5.1 - 10 x ULN</td>
<td>&gt; 10 x ULN</td>
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<tr>
<td>Hyperuricemia (uric acid)</td>
<td>7.5 – 10.0 mg/dL</td>
<td>10.1 – 12.0 mg/dL</td>
<td>12.1 – 15.0 mg/dL</td>
<td>&gt;15.0 mg/dL</td>
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<tr>
<td>Creatinine</td>
<td>1.1 - 1.5 x ULN</td>
<td>1.6 - 3.0 x ULN</td>
<td>3.1 - 6 x ULN</td>
<td>&gt; 6 x ULN or dialysis required</td>
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### URINALYSIS

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<th>Grade 4</th>
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<tr>
<td><strong>Proteinuria</strong></td>
<td>1+ or 200 mg - 1 gm loss/day</td>
<td>2-3+ or 1- 2 gm loss/day</td>
<td>4+ or 2-3.5 gm loss/day</td>
<td>nephrotic syndrome or &gt; 3.5 gm loss/day</td>
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<td><strong>Hematuria</strong></td>
<td>microscopic only &lt;10 rbc/hpf</td>
<td>gross, no clots &gt;10 rbc/hpf</td>
<td>gross, with or without clots, OR red blood cell casts</td>
<td>obstructive or required transfusion</td>
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### RESPIRATORY

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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cough</strong></td>
<td>transient- no treatment</td>
<td>persistent cough; treatment responsive</td>
<td>Paroxysmal cough; uncontrolled with treatment</td>
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<tr>
<td><strong>Bronchospasm, Acute</strong></td>
<td>transient; no treatment; 70% - 80% FEV₁ of peak flow</td>
<td>requires treatment; normalizes with bronchodilator; FEV₁ 50% - 70% of peak flow</td>
<td>no normalization with bronchodilator; FEV₁ 25% - 50% of peak flow; or retractions present</td>
<td>cyanosis: FEV₁ &lt; 25% of peak flow or intubation necessary</td>
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<tr>
<td><strong>Dyspnea</strong></td>
<td>dyspnea on exertion</td>
<td>dyspnea with normal activity</td>
<td>dyspnea at rest</td>
<td>dyspnea requiring Oxygen therapy</td>
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</tbody>
</table>
### CARDIOVASCULAR

<table>
<thead>
<tr>
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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Rhythm</strong></td>
<td>Asymptomatic alterations in EKG (e.g., PR or QT intervals)</td>
<td>asymptomatic, transient signs, no Rx required</td>
<td>recurrent/persistent; symptomatic Rx required</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>transient increase &gt; 20 mm/Hg; no treatment</td>
<td>recurrent, chronic increase &gt; 20mm/Hg./treatment required</td>
<td>acute treatment required; outpatient treatment or hospitalization possible</td>
</tr>
<tr>
<td><strong>Hypotension</strong></td>
<td>transient orthostatic hypotension with heart rate increased by &lt;20 beat/min or decreased by &lt;10 mm Hg systolic BP, No treatment required</td>
<td>symptoms due to orthostatic hypotension or BP decreased by &lt;20 mm Hg systolic; correctable with oral fluid treatment</td>
<td>requires IV fluids; no hospitalization required</td>
</tr>
<tr>
<td><strong>Pericarditis</strong></td>
<td>minimal effusion</td>
<td>mild/moderate asymptomatic effusion, no treatment</td>
<td>symptomatic effusion; pain; EKG changes</td>
</tr>
<tr>
<td><strong>Hemorrhage, Blood Loss (to include blood loss from wound or internal bleeding, including gastrointestinal)</strong></td>
<td>microscopic/occult</td>
<td>mild, no transfusion</td>
<td>gross blood loss; 1-2 units transfused</td>
</tr>
<tr>
<td>NEUROLOGICAL</td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Neuro-Cerebellar</td>
<td>slight incoordination dysdiadochokinesis</td>
<td>intention tremor, dysmetria, slurred speech; nystagmus</td>
<td>locomotor ataxia</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>mild anxiety or depression</td>
<td>moderate anxiety or depression; therapy required; change in normal routine</td>
<td>severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td>subjective weakness no objective symptoms/signs</td>
<td>mild objective signs/symptoms no decrease in function</td>
<td>objective weakness function limited</td>
</tr>
<tr>
<td>Paresthesia (burning, tingling, etc.)</td>
<td>mild discomfort; no treatment required</td>
<td>moderate discomfort; non-narcotic analgesia required</td>
<td>severe discomfort; or narcotic analgesia required with symptomatic improvement</td>
</tr>
<tr>
<td>Neuro-sensory</td>
<td>mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing</td>
<td>moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical</td>
<td>severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)</td>
</tr>
</tbody>
</table>
### Gastrointestinal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>mild or transient; maintains reasonable intake</td>
<td>moderate discomfort; intake decreased significantly; some activity limited</td>
<td>no significant intake; requires IV fluids</td>
<td>hospitalization required;</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 episode in 24 hours</td>
<td>2-5 episodes in 24 hours</td>
<td>&gt;6 episodes in 24 hours or needing IV fluids</td>
<td>physiologic consequences requiring hospitalization or requiring parenteral nutrition</td>
</tr>
<tr>
<td>Constipation</td>
<td>requiring stool softener or dietary modification</td>
<td>requiring laxatives</td>
<td>obstipation requiring manual evacuation or enema</td>
<td>obstruction or toxic megacolon</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>mild or transient; 3-4 loose stools/day or mild diarrhea last &lt; 1 week</td>
<td>moderate or persistent; 5-7 loose stools/day or diarrhea lasting &gt;1 week</td>
<td>&gt;7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or &gt;2L IV fluids required</td>
<td>hypotensive shock or physiologic consequences requiring hospitalization</td>
</tr>
<tr>
<td>Oral Discomfort/Dysphagia</td>
<td>mild discomfort; no difficulty swallowing</td>
<td>some limits on eating/drinking</td>
<td>eating/talking very limited; unable to swallow solid foods</td>
<td>unable to drink fluids; requires IV fluids</td>
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## MUSCULOSKELETAL

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<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arthralgia</strong> (joint pain)</td>
<td>mild pain not interfering with function</td>
<td>moderate pain, analgesics and/or pain interfering with function but not with activities of daily living</td>
<td>severe pain; pain and/or analgesics interfering with activities of daily living</td>
<td>disabling pain</td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>mild pain with inflammation, erythema or joint swelling – but not interfering with function</td>
<td>moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living</td>
<td>severe pain with inflammation, erythema or joint swelling – and interfering with activities of daily living</td>
<td>permanent and/or disabling joint destruction</td>
</tr>
<tr>
<td><strong>Myalgia</strong></td>
<td>Myalgia with no limitation of activity</td>
<td>muscle tenderness (at other than injection site) or with moderate impairment of activity</td>
<td>severe muscle tenderness with marked impairment of activity</td>
<td>frank myonecrosis</td>
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### SKIN

<table>
<thead>
<tr>
<th>Mucocutaneous</th>
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<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema; pruritus</td>
<td>diffuse, maculo papular rash, dry desquamation</td>
<td>vesiculation or moist desquamation or ulceration</td>
<td>exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery</td>
<td></td>
</tr>
</tbody>
</table>

| Induration | < 15mm | 15-30 mm | >30mm |
| Erythema | < 15mm | 15-30 mm | >30mm |
| Edema | < 15mm | 15-30 mm | >30mm |
| Rash at Injection Site | < 15mm | 15-30 mm | >30mm |
| Pruritus | slight itching at injection site | moderate itching at injection extremity | itching over entire body |

### SYSTEMIC

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<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
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<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td>Allergic Reaction</td>
<td>pruritus without rash</td>
<td>localized urticaria</td>
<td>generalized urticaria; angioedema</td>
</tr>
<tr>
<td>Headache</td>
<td>mild, no treatment required</td>
<td>transient, moderate; treatment required</td>
<td>severe; responds to initial narcotic therapy</td>
</tr>
<tr>
<td>Fever: oral</td>
<td>37.7 - 38.5 C or 100.0 - 101.5 F</td>
<td>38.6 - 39.5 C or 101.6 - 102.9 F</td>
<td>39.6 - 40.5 C or 103 - 105 F</td>
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<tr>
<td>Fatigue</td>
<td>normal activity reduced &lt; 48 hours</td>
<td>normal activity decreased 25-50% &gt; 48 hours</td>
<td>normal activity decreased &gt; 50% can’t work</td>
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## APPENDIX E: Common and Infrequent Adverse Events for Study Drugs

### CLINICAL

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ketorolac</th>
<th>Meloxicam</th>
<th>Pregabalin</th>
<th>Opioids</th>
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<tbody>
<tr>
<td>fever</td>
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<tr>
<td>myalgia</td>
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<td>arthralgia</td>
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<tr>
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<tr>
<td>diarrhea</td>
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<td>dyspepsia</td>
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<td>c-difficile colitis</td>
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<td>pseudomembranous colitis</td>
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<td>abdominal pain</td>
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<tr>
<td>altered taste perception</td>
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<td>increased sweating</td>
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<td>pruritus</td>
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<td>superinfection</td>
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<td>urinary tract infections</td>
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Pain Protocol v 9.0 12/22/2014
<table>
<thead>
<tr>
<th><strong>CLINICAL</strong></th>
<th>Ketorolac</th>
<th>Meloxicam</th>
<th>Pregabalin</th>
<th>Opioids</th>
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<tr>
<td>tinnitus</td>
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<td><strong>LABORATORY</strong></td>
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<td>Meloxicam</td>
<td>Pregabalin</td>
<td>Opioids</td>
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APPENDIX F: CONSENT TEMPLATE

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH

INFORMED CONSENT DOCUMENT

Patient Consent Form

Study Title: Improving Pain Management and Long Term Outcomes Following High Energy Orthopedic Trauma (Pain Study)

Principal Investigator: Renan Castillo, PhD

IRB No.: 00004559

PI Version Date: December 22, 2014

You are being asked to volunteer to be a part of a research study. Please read this form carefully before you sign it. This consent form explains the research study and your part in the study. If you decide not to participate in this study there will be no impact on your medical care. You can choose not to take part and if you join, you may quit at any time. Ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand. Ask as many questions as needed. All of your questions should be answered to your satisfaction before you sign this form.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

The purpose of this research study is to test different ways of treating pain that results from orthopedic (bone) injury. We believe that by using different types of medicines before and during bone surgery we can achieve better control of patient pain without causing more side effects.

Researchers do not know whether using a non-steroidal anti-inflammatory drug (NSAIDS) or gabapentenoid on top of your normal pain treatment will make it easier to treat your pain. In this study, we are trying to answer this question. All participants will continue to receive the pain medications orthopedic patients normally receive in addition to the study medicine. In addition, we are going to place participants in three groups: one will receive NSAIDS, one will receive a gabapentenoid, and one will receive a placebo, or sugar pill. Neither you nor your doctor will know whether you are getting the treatment drug or the placebo. This study is designed to test the differences between these types of treatments to help find out the best way to manage pain.

Additionally, some patients who experience ankle injuries go on to develop post-traumatic osteoarthritis (PTOA). As part of a pilot study, we are also following a smaller number of these patients.
patients and taking radiographic images of their injury over time to see if we can find out what types of injuries are more likely to develop PTOA.

The Pain study is funded by the Department of Defense (DOD) and is being carried out in more than 25 major trauma centers across the United States.

2. **WHY AM I BEING ASKED TO PARTICIPATE?**

You are being asked to participate in this study because you are between the ages of 18 to 80 and have a broken bone that your surgeon has determined is bad enough to qualify for the study. People like you who are being treated at major trauma centers from around the county are being asked to participate. You are one of over 495 patients expected to join the Pain study.

3. **HOW LONG WILL THE STUDY LAST?**

If you agree to participate in this study, you will be followed for up to a year after your injury. If you have an ankle injury that qualifies for the pilot study and you agree to participate, you will be agreeing to be followed up for one additional study visit two years following the surgical repair of your injury.

4. **HOW DOES THE STUDY WORK?**

If you agree to participate in the Pain study, you will be assigned by chance (like flipping a coin), to one of the three types of treatment being studied:

- **Group A:** Standard of Care + Placebo: Normal, standard of care pain management prescribed by your surgeon plus two weeks of oral placebo (sugar) pills, followed by intravenous and oral placebo treatment for up to 48 hours after surgical repair of your injury.
- **Group B:** Standard of Care + NSAID: Normal, standard of care pain management prescribed by your surgeon plus up to two weeks of oral Meloxicam pills (17.5 mg pill, taken twice a day), until the time of your surgery, followed by intravenous ketorolac and oral placebo treatment for up to 48 hours after surgical repair of your injury.
- **Group C:** Standard of Care + gabapentenoid: Normal, standard of care pain management prescribed by your surgeon plus up to two weeks of oral pregabalin pills (175 mg pill, taken twice a day), until the time of your surgery, followed by intravenous placebo and oral pregabalin treatment for up to 48 hours after surgical repair of your injury.

You have an equal chance of getting any of the treatments. We are using this method for deciding which treatment you will get because it is not clear at the present time which treatment is better for you and people like you with similar injuries.
As part of the study, neither you nor your surgeon will know which group you are assigned to because all the pills will look the same. You will begin receiving the oral treatment immediately after you are enrolled. If you are discharged from the hospital before your final surgery, you will go home with the medication and continue to take it two times a day until either you finish all the medication or you return to the hospital, whichever comes first. During this time, you will also be able to take any other medications your surgeon thinks would be helpful to manage your pain and you think you need. Your medication package will include a log. Every day you are not in the hospital, for the next two weeks, you will record your pain score in the morning and evening and whether or not you took your study medication. You will also use this book to tell us about any health problems you have with your pain medications.

When it is time for your surgery, you will stop taking the oral medications you were given when you enrolled, and you will be given intravenous medication and a pill before the surgery. This treatment will continue for 48 hours after the surgery or until you are discharged from the hospital. You will also be asked questions about any side effects you may be experiencing, both during your time taking the oral medication and during the time surrounding your surgery.

When you come back for normal follow-up visits to see your surgeon 3, 6 and 12 months after your injury, you will also complete a 15-30 minute interview where you will be asked questions about what you are doing most of the time, your pain, your feelings, and how your recovery is going. If you are not able to come back, we may contact you by telephone to do these interviews.

Any CT scans or X-rays that are taken during this study as part of your normal treatment will be shared with the study team, up until 24 months following your surgery. Additionally, if you agree to participate in the pilot study, you may be asked to return to the hospital for an additional CT scan up to 3 months following your surgery and for an additional X-ray 24 months following your surgery.

At the end of the study, we will also obtain a copy of your hospital billing records for all hospitalizations which occur between your injury and a year after your injury. This will help us understand differences in costs of care for different types of patients.

5. WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS?

The risks of being in this study are primarily related to side effects commonly seen with the medications being studied.

- **Group A**: Standard of Care + Placebo: There are no increased risks if you are assigned to this group. You will receive the exact same medicine as you would if you were not in the study.

- **Group B**: Standard of Care + NSAID: Although observed infrequently, the most common side effects associated with NSAIDS include kidney problems, low white blood cell counts, and bleeding more than normal.
Additionally, it is believed that NSAIDS may also be associated with possible failure of your bone to heal. One of the goals of the study is to determine whether these effects actually happen when people take these medications.

- **Group C**: Standard of Care + gabapentenoid: Although observed infrequently, the most common side effects associated with gabapentenoids include sleepiness, dizziness, headaches, clumsiness, swelling of the hands and feet, visual changes, and dry mouth.

6. **WHAT ARE THE POTENTIAL BENEFITS?**

You will not benefit directly from your participation in this study, although if you are assigned to a medication group, you may experience decreased pain due to your injury. Your participation in the study could help us determine the best treatment for injuries like yours. This information could be very helpful to other people who have this same injury in the future.

7. **DO I GET ANY PAYMENT FOR BEING IN THE STUDY?**

You will receive $25 for returning your medication blister packaging. You will also receive $25 for completing each of the first 2 follow-up visits and $50 for completing the final visit at 12 months after your injury, for a total of $125. If you complete these interviews by phone you will still receive the payment. These payments are in appreciation of your time and effort. If you are selected to be in the PTOA pilot study and agree to participate, you will receive $25 for the study CT scan and $25 for the study X-ray at 24 months after your surgery.

8. **ARE THERE ANY COSTS INVOLVED IN BEING IN THE STUDY?**

There are no additional costs for taking part in this research study above the reasonable and customary costs of caring for patients with injuries like yours who are not in the study. The cost of the medications given as part of the study will be paid for by the study.

9. **WILL MY INFORMATION BE KEPT PRIVATE?**

By signing this form, you give permission for your health information to be used and shared for the purposes of this study. All research projects carry some risk that information about you may become known to people outside of the study. <<Insert Clinical Center Name>> has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it. We will keep your records in a secure place. Only clinical center staff or people authorized to audit the study will have access to the study forms. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The people working on the study at this clinic will collect information about you. This includes things learned from the procedures described in this consent form and other information.
including your name, contact information (such as address) and personal health information (such as lab results, diagnoses, medications, etc.). Your name and other identifying information will be kept private. We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study. Generally, only people on the research team will know that you are in the research study and will see your information. A unique number and special code will be used in place of your name for data entry. The number and code cannot be linked to your name except at the clinical center where you complete visits. Data collected from your study visits will be labeled with only the unique number and special code. Study data will be sent to the Data Coordinating Center at Johns Hopkins University, in Baltimore, Maryland.

You may cancel your decision to share your health information at any time by contacting the study coordinator or director using the information included in item #14 below. After the study personnel receive your cancellation, no new information will be collected about you. If you cancel, the research team will still be allowed to use the information that was collected prior to your cancellation.

10. WILL YOU SHARE MY INFORMATION WITH OTHERS?

We will use your information only for the purposes of this study. The data from the study may be published. However, you will not be identified by name. People designated from the institutions where the study is being conducted will be allowed to inspect sections of your medical and research records related to the study. This includes people designated by The Johns Hopkins Bloomberg School of Public Health who are overseeing this study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

The Department of Defense is providing funding to sponsor this study. Representatives from the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP) Human Research Protections Office (HRPO) may have access to research records in their role to protect human subjects engaged in research.

11. WHAT ARE MY ALTERNATIVES TO PARTICIPATION?

Your alternative is to not take part. If you choose not to take part, your healthcare will not be affected.

12. WHAT HAPPENS IF I LEAVE THE STUDY EARLY?

Your participation in this study is completely voluntary. You have the right to withdraw from the research study at any time without penalty. Your decision will not affect the medical care you
receive. If you decide to stop participating, you should notify the study doctor or the research coordinator at your center.

Your participation in this research study could be ended without your consent. Possible reasons could include our decision to end the study early or other reasons.

13. WHAT HAPPENS IF I AM INJURED OR BECOME ILL BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or become ill because of your participation in this study, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be billed for any other medical care. If you have any costs that are not covered by insurance, they are your responsibility.

You do not give up any of your legal rights by signing this form. You can seek legal compensation for any injury that may occur to you during the study as a result of an error by a member of the research staff or others.

14. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

- <<insert name>>, the study coordinator at your hospital has discussed this information with you and offered to answer any questions you may have. If you have further questions or get sick or injured as a result of being in this study, you can contact << insert him/her >> at <<telephone number>>. You may also call the Director of the Study at your hospital, <<insert name>>, at <<telephone number>>.
- If you have further questions about your rights as a study participant you can call or contact the Johns Hopkins Bloomberg School of Public Health IRB Office. The Johns Hopkins Bloomberg School of Public Health is serving as the overall coordinating center for this study that is being conducted in hospitals around the country. Contact the Johns Hopkins IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

  Address:  Johns Hopkins Bloomberg School of Public Health
  615 N. Wolfe Street, Suite E1100
  Baltimore, MD  21205
  Telephone: 410-955-3193
  Toll Free: 1-888-262-3242
  Fax: 410-502-0584
  E-mail:  irboffice@jhsph.edu

What does your signature (or thumbprint/mark) on this consent form mean?

Your signature (or thumbprint/mark) on this form means:
• You have been informed about this study’s purpose, procedures, possible benefits and risks.
• You have been given the chance to ask questions before you sign.
• You have voluntarily agreed to be in this study.

Additionally, by checking and initialing here, you agree to be contacted up to three months from now to consider participating in the PTOA pilot study (Ankle fractures only).

______________ Initials  □  Check here if you agree to be contacted.

________________________   _____________________________   __________
Print name of Adult Participant    Signature of Adult Participant    Date

Ask the participant to mark a “left thumb impression” in this box if the participant is unable to provide a signature above.

________________________   _____________________________   __________
Print name of Person Obtaining    Signature of Person Obtaining Consent    Date
Consent

Give one copy to the participant and keep one copy in study records
You are being asked to volunteer to be a part of a research study. Please read this form carefully before you sign it. This consent form explains the research study and your part in the study. If you decide not to participate in this study there will be no impact on your medical care. You can choose not to take part and if you join, you may quit at any time. Ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand. Ask as many questions as needed. All of your questions should be answered to your satisfaction before you sign this form.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

The purpose of this research study to know if we can look at images of a broken bone and predict who will go on to develop post-traumatic osteoarthritis, or PTOA. Researchers believe that as many of half of patients with the kind of injury you experienced go on to develop this lifelong condition. We believe that we can identify who may develop PTOA by examining images of the injury and its repair, using CT scans and X-rays, as well as patient reported pain and function.

When a person develops PTOA, they often experience more pain than other people with similar injuries. At this point, there are no ways of preventing or effectively treating PTOA. We hope that through this study we will develop the tools to identify people at highest risk of developing PTOA and use that information to find ways to prevent PTOA in the future.

The PTOA study is funded by the National Institutes of Health as a pilot study of the Pain study and is being carried out in more than 25 major trauma centers across the United States.

2. WHY AM I BEING ASKED TO PARTICIPATE?
You are being asked to participate in this study because you are currently a participant in the Pain study and you provided permission to be contacted for this pilot study. Your injuries are the type that is more likely to develop PTOA.

3. HOW LONG WILL THE STUDY LAST?

If you agree to participate in this study, you will be asked to come to the hospital for a CT scan up to three months after your last surgery and you agree to another study visit two years later for an X-ray and short interview.

4. HOW DOES THE STUDY WORK?

If you agree to participate in the PTOA study, you will agree to:

- CT Scan: One CT scan to be completed within the next two weeks, paid for by the study.
- X-ray: An additional series of x-rays to be completed 24 months following surgical repair of your injury, paid for by the study.
- Interview: A short interview rays to be completed 24 months following surgical repair of your injury.

Participating in this study does not affect your participation in the Pain study, and you will continue to participate in Pain interviews and follow-up visits even if you enroll in this study, too.

5. WHAT ARE THE POTENTIAL RISKS OR DISCOMFORTS?

In this study, you will be exposed to radiation called "ionizing radiation," which is like x-rays. While CT scans are routinely obtained to evaluate a number of musculoskeletal conditions, they expose patients to more radiation than other forms of imaging. The amount of radiation you will get in the study is 15 mrem for the CT scan and 1 mrem for the X-ray. (A “mrem” is how we measure radiation dose.) In comparison, one regular chest x-ray would give you 10 mrem. The natural radiation we are exposed to all the time — like from the sun — gives you about 300 mrem each year.

Neither chest x-rays nor background radiation have been found to harm most healthy adults. The main potential risk from exposure to radiation is cancer. This could appear decades from now. The risk of getting cancer from radiation depends on how much radiation you are exposed to. The risk of dying from cancer due to the radiation exposure in this study is 88/100,000. In comparison, 4 out of every 10 people will get cancer in our lifetime. And, 2 out of every 10 of us will die from cancer.
Tell us now if you have been in other research studies where you had ionizing radiation. Also tell us if you have been exposed to radiation in other ways, like on your job or in radiation therapy.

If you take part in a research study that includes a medical procedure, you must be willing to have a pregnancy test done before each procedure. You may not participate in this study if you are pregnant at the time the CT scan would be performed.

6. WHAT ARE THE POTENTIAL BENEFITS?

You will not benefit directly from your participation in this study. However, your participation in the study could help us determine who is most likely to develop PTOA if they have injuries like yours. This information could be very helpful to other people who have this same injury in the future.

7. DO I GET ANY PAYMENT FOR BEING IN THE STUDY?

If you participate in this study, you will receive an additional $25 for each additional visit you complete to compensate you for your time, for a total of $50 ($25 following the CT scan, and an additional $25 following your final visit at 24 months).

8. ARE THERE ANY COSTS INVOLVED IN BEING IN THE STUDY?

There are no additional costs for taking part in this research study. The study will cover the costs of the additional CT scan and X-rays.

9. WILL MY INFORMATION BE KEPT PRIVATE?

By signing this form, you give permission for your health information to be used and shared for the purposes of this study. All research projects carry some risk that information about you may become known to people outside of the study. <<Insert Clinical Center Name>> has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it. We will keep your records in a secure place. Only clinical center staff or people authorized to audit the study will have access to the study forms. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The people working on the study at this clinic will collect information about you. This includes things learned from the procedures described in this consent form and other information including your name, contact information (such as address) and personal health information (such as lab results, diagnoses, medications, etc.). Your name and other
identifying information will be kept private. We cannot do this study without your permission to use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study. Generally, only people on the research team will know that you are in the research study and will see your information. A unique number and special code will be used in place of your name for data entry. The number and code cannot be linked to your name except at the clinical center where you complete visits. Data collected from your study visits will be labeled with only the unique number and special code. Study data will be sent to the Data Coordinating Center at Johns Hopkins University, in Baltimore, Maryland.

You may cancel your decision to share your health information at any time by contacting the study coordinator or director using the information included in item #14 below. After the study personnel receive your cancellation, no new information will be collected about you. If you cancel, the research team will still be allowed to use the information that was collected prior to your cancellation.

10. WILL YOU SHARE MY INFORMATION WITH OTHERS?

We will use your information only for the purposes of this study. The data from the study may be published. However, you will not be identified by name. People designated from the institutions where the study is being conducted will be allowed to inspect sections of your medical and research records related to the study. This includes people designated by The Johns Hopkins Bloomberg School of Public Health who are overseeing this study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

The National Institutes of Health is providing funding to sponsor this study. Federal and your local IRB may have access to research records in their role to protect human subjects engaged in research.

11. WHAT ARE MY ALTERNATIVES TO PARTICIPATION?

Your alternative is to not take part. If you choose not to take part, your healthcare will not be affected.

12. WHAT HAPPENS IF I LEAVE THE STUDY EARLY?

Your participation in this study is completely voluntary. You have the right to withdraw from the research study at any time without penalty. Your decision will not affect the medical care you receive. If you decide to stop participating, you should notify the study doctor or the research coordinator at your center.
Your participation in this research study could be ended without your consent. Possible reasons could include our decision to end the study early or other reasons.

13. WHAT HAPPENS IF I AM INJURED OR BECOME ILL BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or become ill because of your participation in this study, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of care, just as you would be billed for any other medical care. If you have any costs that are not covered by insurance, they are your responsibility.

You do not give up any of your legal rights by signing this form. You can seek legal compensation for any injury that may occur to you during the study as a result of an error by a member of the research staff or others.

14. WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

- <<insert name>>, the study coordinator at your hospital has discussed this information with you and offered to answer any questions you may have. If you have further questions or get sick or injured as a result of being in this study, you can contact <<insert him/her>> at <<telephone number>>. You may also call the Director of the Study at your hospital, <<insert name>>, at <<telephone number>>.
- If you have further questions about your rights as a study participant you can call or contact the Johns Hopkins Bloomberg School of Public Health IRB Office. The Johns Hopkins Bloomberg School of Public Health is serving as the overall coordinating center for this study that is being conducted in hospitals around the country. Contact the Johns Hopkins IRB if you feel you have not been treated fairly or if you have other concerns. The IRB contact information is:

  Address: Johns Hopkins Bloomberg School of Public Health
  615 N. Wolfe Street, Suite E1100
  Baltimore, MD 21205

  Telephone: 410-955-3193
  Toll Free: 1-888-262-3242
  Fax: 410-502-0584
  E-mail: irboffice@jhsph.edu
What does your signature (or thumbprint/mark) on this consent form mean?

Your signature (or thumbprint/mark) on this form means:

- You have been informed about this study’s purpose, procedures, possible benefits and risks.
- You have been given the chance to ask questions before you sign.
- You have voluntarily agreed to be in this study.

________________________   _____________________________   __________

Print name of Adult Participant   Signature of Adult Participant   Date

________________________   _____________________________   __________

Print name of Person Obtaining Signature of Person Obtaining Consent   Date

Consent

Give one copy to the participant and keep one copy
APPENDIX H: EVALUATION TO GIVE CONSENT

EVALUATION TO GIVE CONSENT

Procedure: Make a subjective judgment regarding item 1 below. Ask questions 2 through 5. You may select the language to use in asking the questions in order to help the respondent understand them.

1. Is the respondent alert and able to communicate with you?

   Yes ___   No ____  (if condition not likely to change, patient ineligible)

2. Ask the respondent to name at least one thing that s/he will be asked to do as part of the study.

   Describe ____________________________________________________________
   ____________________________________________________________________

3. Ask the respondent to explain how it will be decided which treatment s/he will get if s/he decides to join the study.

   Describe ____________________________________________________________
   ____________________________________________________________________

4. Ask the respondent to explain what s/he could do if s/he decided s/he did not want to participate in the study.

   Describe ____________________________________________________________
   ____________________________________________________________________

5. Ask the respondent to explain what s/he would do if s/he were experiencing distress or discomfort at any time during the study.

   Describe ____________________________________________________________
   ____________________________________________________________________

I hereby certify that the above-named respondent is alert, able to communicate, and able to give acceptable answers to items 2, 3, 4 and 5 above.

__________________________________________________________  ________________
Research Coordinator                                      Date

Pain Protocol v 9.0 12 22 14
APPENDIX I: STUDY INSERT

HEADLINE: Be part of the solution. Help advance limb trauma care through research.

Your participation in the Pain study can help decide the best treatment for future patients who have injuries just like yours.

What is the PAIN study?

The purpose of this research study is to test different ways of treating pain that results from orthopedic (bone) injuries. We believe that by using small amounts of different types of medicines before and during bone surgery we can achieve better control of patient pain without causing more side effects. That is why we need your help . . . the Pain study will help determine which type of treatment is best.

Who can be in this study?

Over 495 patients around the country are expected to join the Pain Study. You are being asked to join because you are between the ages of 18 to 80 and have a fracture of your ankle that your surgeon believes may qualify you for the study. People like you who are being treated at major trauma centers from around the county are being asked to participate.

How does the study work?

If you choose to take part in the Pain study, you will be assigned by chance (like flipping a coin), to one of the three types of treatments. You have a 1/3 chance of getting any one treatment. We are using this method for deciding which treatment you will get because it is not clear at the present time which treatment is better for you and people like you with similar injuries.

The three treatment types are:

- **Group A, Standard of Care + Placebo:** Normal, standard of care pain management prescribed by your surgeon plus two weeks of oral placebo (sugar) pills, followed by intravenous and oral placebo treatment for the 48 hours after surgical repair of your injury.

- **Group B, Standard of Care + NSAID:** Normal, standard of care pain management prescribed by your surgeon plus up to two weeks of oral Meloxicam pills (one 7.5 mg pill, taken twice a day), until the time of your surgery, followed by intravenous ketorolac and oral placebo treatment for the 48 hours after surgical repair of your injury.

- **Group C, Standard of Care + gabapentenoid:** Normal, standard of care pain management prescribed by your surgeon plus up to two weeks of oral pregabalin pills (one 75 mg pill, taken twice a day), until the time of your surgery, followed by intravenous placebo and oral pregabalin treatment for the 48 hours after surgical repair of your injury.
After your surgery, your care will be exactly the same as if you were not participating in the study. You will come back to see your doctor after your surgery. At each follow-up your doctor will examine your leg and see how well the fracture is healing. We will also ask how you are doing overall.

We hope you will consider taking part in this study. It is a way to help be part of the solution and help advance limb trauma care for others in the future. Please talk to your doctor about taking part, or visit www.METRC.org to learn more.
### Narrative

You are watching this video because you have a bad ankle fracture. This injury is quite commonly seen in both civilian trauma patients and among members of the military. For this reason, the United States Department of Defense is funding research to help us determine the best way to treat pain from these injuries. The goal of this research is to help civilians and wounded service members alike recover from ankle injuries like yours and return to their normal activities. Today, we are asking you to consider participating in this research to help people like you in the future.

The name of this research study is Improving pain management and long term outcomes following high energy orthopaedic trauma, or the PAIN study. This video will give you more information to help you decide if you would like to participate in this study.

The goal of the PAIN study is to help us find the best way to treat pain associated with a badly broken ankle. These injuries can be extremely painful because there is often injury to the skin, muscle, and soft tissue around the bone. We know that for patients who experience excessive pain their injuries often tend to do worse in their recovery, even many years after.

Right now the most common way to treat pain is with opioids. Opioid use may lead many side effects, including nausea and trouble with breathing. Also, opioid use over the long term can lead to opioid dependence. Another problem is that even with increased opioid use, many patients are still not getting enough

### Suggestions for Visuals

- METRC logo
- Image of service members
- Image of moderate fractures of the pilon/calcaneus

---

Pain Protocol v 9.0 12 22 14
pain control.

We are trying to find a better way to manage pain. That is why we need your help. The PAIN study will determine whether the addition of other types of standard pain medications for pain treatment, in addition to the pain treatment your doctor would normally prescribe, is better.

In this study we are looking at three possible ways to treat your pain. One treatment is the normal pain care that you would receive with no additional study medication. This is the same as you would get if you do not enroll in the study. Another treatment is your normal pain care plus the use of non-steroidal anti-inflammatory drugs (NSAIDs), similar to over-the-counter pain medications that you may be familiar with, like ibuprofen. Lastly, the third treatment we are looking at is adding a drug called pregabalin, or Lyrica, which is normally used for pain that affects your entire body.

The drugs we are looking at adding to your normal pain treatment are not new and are often used to treat pain. However, their ability to help manage pain like yours has not been fully evaluated.

ENTER DR. . . .

I’m Dr. Allan Gottschalk, an anesthesiologist at the Johns Hopkins Medical Institution’s Department of Anesthesiology and Critical Care Medicine. YOU are being asked to participate in the PAIN study because your doctor has determined that you qualify for this study due to your type of injury. This study’s success depends on people with injuries like yours from major trauma centers across the country joining together to take part in this effort. I’m going to describe what you can
expect if you decide to join this study.

It is important to understand that this is a randomized study. If you agree to participate, you will receive one of the three types of treatments described earlier. The treatment you receive will be picked for you by chance. This is like pulling a card from a deck with only three types of cards, and means you will have an equal chance of receiving one of the three treatments. This helps us make sure that an equal number of similar people and injuries in the study are getting each treatment. The rest of your medical care will be the same as if you were not in the study. The only effect the study will have is in choosing which of the three treatments you receive.

ALLAN VOICE:

After your surgery, you will have follow-up appointments with your surgeon at the same times you would if you were not in the study. These follow-up visits will be at 3, 6, and 12 months after your injury. At each of these visits, your doctor will see how well the broken ankle is healing and see if you have any pain. During these visits, a member of the research team will ask you some questions to find out how you are doing overall. These questions take about 15 to 20 minutes to answer and are typically asked when you are waiting to meet with your surgeon.

NARRATOR

Now, let’s look more closely at what you will be asked to do if you join the PAIN study.

Just like everyone else in the study, your doctor will manage your pain using the same medicine you would be given if you were not in the study.
While you are in this study, no one will know which group you are in, including you, your nurse and your doctor. Like everyone in the study, you will take two pills per day, starting now, for up to two weeks from now. You will stop taking these pills when your surgeon repairs your fracture. These pills may or may not contain Lyrica or the NSAID meloxicam, or they may not contain any additional pain medicine, depending on which treatment group you are in.

Some people with injuries like yours go home before their fracture is repaired. If this is the case for you, you will continue to take these pills at home. There is space on the package of pills to record the time you take each pill, any pain you may have, and any side effects you may experience. We will ask that you bring back the package of pills when you return to the hospital to have your fracture repaired. If your fracture is repaired before you leave the hospital, your medical team will oversee giving you the medicine and recording this information for you.

Every time you have a surgery, including when your surgeon repairs your fracture, you will take two pills before the surgery and a pill twice a day for two days after the surgery. Also, you will receive intravenous medication before surgery and for two days afterwards. The content of these medications will be specific to the group you are randomly assigned to.

During this entire time, your doctor will provide pain medicine like he or she would normally do, whether you were in the study or not.

Additionally, to understand your treatment images of x-rays

| Picture of person taking medicine at home, preferably from a blister pack | Picture of person being given pill in hospital bed | Picture of pt getting IV meds | Images of x-rays |
better we will collect images such as x-rays and CT scans. The images will be de-identified which means none of your personal information will be included in them.

We would like to remind you that in the PAIN study you will be able to take your normal pain medications, with the exception of NSAIDs such as ibuprofen (advil and motrin), naproxen sodium (aleve), celecoxib and aspirin). This study is to see if additional medication can help you.

We hope that the description of the three treatments has helped you better understand the Pain study. Despite many years of research, there’s still much we do not know about treating pain following orthopaedic injury. This is why trauma centers and patients throughout the country are joining together in an effort to find the best pain treatment for injuries like yours. Our goal is to help people with these severe injuries recover and get back to doing what they enjoy most in life.

If you have questions about these treatments or the study, please ask your surgeon or study coordinator at the end of this video.

Thank you for considering taking part in the PAIN study. Previous research volunteers have provided us with tremendous knowledge that will directly benefit you in the care we give you today. We are asking you to consider participating in this study to help civilians and injured soldiers in the future. If you decide to join the PAIN study, know that you will be helping to shape the future of trauma care.

Thank you, again, for learning more about the PAIN study, and we wish you the best in your recovery.
APPENDIX K: PATIENT DAILY LOG

Page 1

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Please take one pill each morning and each evening. Record your pain score on a scale of 0 (no pain) to 10 (the worst pain you can imagine) and the time you take the pill. **While you are taking study medications, you cannot take ANY other non-steroidal anti-inflammatory medication (e.g. ibuprofen (Advil, Motrin), naproxen sodium (Aleve), celecoxib (Celebrex), aspirin, etc). If you are not sure whether a medication is allowed or not, contact _____________________.

<table>
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<tr>
<th>Day 1</th>
<th>Pain Score</th>
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Appendix L: Patient Education Materials (Trifold brochure)Page 1:

Please do not forget to...

- Bring the Blister Pack back when you return to the hospital for your surgery.
- The blister pack may contain extra pills if you return to the hospital in fewer than 14 days.
- Write down side effects and pain level on diary.

DO NOT TAKE ANY NSAIDS WHILE PARTICIPATING IN THIS STUDY!

EXAMPLES OF NSAIDS ARE:

- IBUPROFEN (ADVIL AND MOTRIN)
- NAPROXEN SODIUM (ALEVE)
- CELECOXIB (CELEBREX)
- ASPIRIN

Welcome to the Pain Study

PAIN Study

METRC
Major Extremity Trauma Research Consortium (METRC)

624 N. Broadway
Baltimore, MD 21205
Emergency/Debriefing Information Call: 888-562-6444

HOW TO USE THE MEDICATION BLISTER PACK

Inside this pamphlet is information on how to use the Pain Study blister pack once you get home.

Page 2
The Pain Study

We appreciate your support of the Pain Study, which will further research to improve treatment for people with injuries like yours.

In this pamphlet we provide information about how to use the blister pack that contains your study medications.

Please take some time to look over this pamphlet before taking the blister pack home.

Medication Instructions

While you are in the hospital, all your medicine will be given to you by your nurse. But when you go home, you will need to continue to take the study medicine from the blister pack from the time you go home until you return to the hospital.

At home, you will take one pill from the blister pack two times a day.

Once in the morning:

And once at night.

You may finish the medicine before you come back to the hospital.

Please keep the package for when you return to the hospital.

Recording Information

Each time you take a pill please write down how much pain you feel and what time you took your pill.

Every day, you will also mark any symptoms or side effects you think you may be having as a result of taking these pills.

For a $25 gift card, please return the blister pack with any unused medicine to the study coordinator when you return to the hospital. (It is ok if there are leftover pills)