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

Renan C. Castillo, PhD, Srinivasa N. Raja, MBBS, MD,† Katherine P. Frey, RN, MPH,* Heather A. Vallier, MD,‡ Paul Tornetta III, MD,§ Todd Jaeblon, DO,‖ Brandon J. Goff, DO,¶ Allan Gottschalk, MD, PhD,† Daniel O. Scharfstein, ScD,** Robert V. O'Toole, MD,†† and METRC*

Summary: Poor pain control after orthopaedic trauma is a predictor of physical disability and numerous negative long-term outcomes. Despite increased awareness of the negative consequences of poorly controlled pain, analgesic therapy among hospitalized patients after orthopaedic trauma remains inconsistent and often inadequate. The Pain study is a 3 armed, prospective, double-blind, multicenter randomized trial designed to evaluate the effect of standard pain management versus standard pain management plus perioperative nonsteroidal anti-inflammatory drugs or pregabalin in patients of ages 18–85 with extremity fractures. The primary outcomes are chronic pain, opioid utilization during the 48 hours after definitive fixation and surgery for nonunion in the year after fixation. Secondary outcomes include preoperative and postoperative pain intensity, adverse events and complications, physical function, depression, and post-traumatic stress disorder. One year treatment costs are also compared between the groups.

Key Words: pain management, opioids, nonunion, randomized trial

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BACKGROUND AND RATIONALE

Perioperative pain that can persist and become chronic is common after orthopaedic trauma. Short- and long-term pain after orthopaedic trauma predicts physical disability, delayed return to work, psychological distress, low satisfaction with health care, and failure to participate in physical therapy.[1–3] Despite increased awareness of the negative consequences of poorly controlled pain, analgesic therapy among hospitalized patients remains inconsistent and often inadequate.[4,5] Several studies have also shown a strong, and potentially etiological link between pain immediately after injury and subsequent depression and post-traumatic stress disorder (PTSD). In one study, an increase of one-half SD in in-hospital pain intensity was associated with a 7-fold increase in the odds of having PTSD at 8 months post-discharge.[6] In the LEAP study of high-energy lower extremity trauma, pain early in the recovery period after severe extremity trauma was the single largest predictor of long-term chronic pain 5–10 years after injury.[7]

Opioids are currently administered at the time of trauma resuscitation, preoperatively, during general and regional anesthesia as a component of the anesthetic itself, and to initiate postoperative analgesia. Opioid-related side effects include nausea, vomiting, constipation, pruritis, miosis, sedation, and respiratory depression that can lead to in-hospital mortality.[8] All opioids depress respiratory drive depending on dose, patient comorbidities, and other drug therapy, increasing risks to patient safety. In addition, opioids can result in opioid tolerance and/or hyperalgesia. Nationally, an epidemic in opioid-related addiction, overdoses, and deaths[9] has led to calls for improved prescribing guidelines[10] and more proactive approaches to addressing the potential for misuse.[11] The increasing concern regarding the adverse effects of opioid analgesics has also highlighted the potential benefits of multimodal analgesia. The theory is that the additive or synergistic effects of different classes of analgesics will result in lower doses needed of individual drugs, with fewer adverse effects from any individual medication. Fewer side effects and improved analgesia have been demonstrated with certain multimodal analgesia techniques, resulting in shorter hospitalizations, enhanced recovery, and decreased health care costs.[12] While numerous drugs have been studied, the alpha-2-delta receptor modulators (gabapentinoids) and nonsteroidal anti-inflammatory drugs (NSAIDs) have few adverse effects and remain promising adjuvant systemic drugs for perioperative pain management. However, the effectiveness and safety of these agents have not been adequately studied in orthopaedic trauma patients. A recent meta-analysis of 13 randomized trials[13] confirmed previous findings that perioperative use of the NSAID ketorolac is effective at reducing both pain and opioid consumption, and

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From the *Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; †Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine; ‡Department of Orthopaedics, The MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH; §Department of Orthopaedic Surgery, Boston University Medical Center, Boston, MA; ‖Department of Orthopaedic Surgery, Louisiana State University Health Shreveport, Shreveport, LA; ¶Department of Pain Management, Brooke Army Medical Center, San Antonio, TX; **Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; and ††R Adams Cowley Shock Trauma Center, Department of Orthopaedics, University of Maryland School of Medicine, Baltimore, MD.

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Reprints: Renan C. Castillo, PhD, Johns Hopkins Bloomberg School of Public Health, 624 N Broadway, 5th Floor, Baltimore, MD 21205 (e-mail: rcastil1@jhu.edu).

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a meta-analysis of 27 studies found no evidence of perioperative bleeding after multimodal ketorolac use among surgical patients.[14] However, concerns about renal impairment, gastrointestinal irritation, and platelet inhibition constrain usage and limit the dose and duration of NSAID administration. More directly relevant to fracture care, NSAIDs in general and ketorolac, in particular, have been shown in animal models to impair osteogenesis at high doses.[15,16] Other animal studies have demonstrated variability in muscle and ligamentous injury healing with ketorolac.[17,18] Human studies of spinal fusion offer mixed results, with 48 hours of ketorolac showing no effect on the fusion rate, but longer duration therapy, even at lower doses, seems to reduce the fusion rate.[19,20] Few data exist regarding fracture healing in orthopaedic trauma, though one trial of long-term NSAID use demonstrated surprisingly high rates of nonunions.[21] Therefore, concern about bone formation remains a major barrier to the use of NSAIDs for multimodal perioperative pain management in this population, despite a lack of high-grade clinical evidence that short courses of NSAIDS are problematic.

Gabapentin has been FDA-approved for the treatment of postherpetic neuralgia, and recommended as a first-line drug for neuropathic pain. A newer analog, pregabalin, has also demonstrated efficacy in the management of many chronic pain states and is approved in the United States for use in postherpetic neuralgia, painful diabetic neuropathy, and fibromyalgia.[22,23] Over the last decade, 22 RCTs have investigated postoperative pain management with gabapentin in more than 1900 patients, and 8 studies have examined the effects of pregabalin in about 700 surgical patients. Meta-analysis and critical reviews conclude that gabapentin and pregabalin provide better postoperative analgesia than placebo, reducing opioid consumption in the first 24 hours postsurgery by 20%–62%, or by 25–30 mg of morphine. However, only 2 of these studies included orthopaedic procedures, and follow-up was limited to the immediate postoperative period (up to 7 days), with only 7 following patients from 1 to 3 months postinjury.[24–26] Furthermore, pain with movement was evaluated in only one-half of the studies. A more recent review of 17 randomized trials of pregabalin alone found improved analgesia, despite side effects without severe clinical consequence.[27] A handful of recent randomized trials in elective orthopaedic patients suggest a similar pattern. A small randomized trial showed improvements in both pain and functional outcome among patients receiving perioperative gabapentinoids for lumbar discectomy,[28] although this study may have been underpowered.

The aims of this study are to: (1) evaluate the effect of standard pain management versus standard pain management plus perioperative NSAIDs in a patients with extremity fractures; (2) evaluate the effect of standard pain management versus standard pain management plus perioperative pregabalin; and (3) estimate the incremental cost-effectiveness of each adjunctive analgesic therapy relative to standard of care analgesic therapy. It is hypothesized that compared with patients who receive standard of care pain management, patients who are treated with NSAIDS and patients who receive pregabalin will have reduced postoperative opioid utilization, reduced levels of persistent pain, and noninferior rates of surgery for nonunion.

METHODS: TRIAL DESIGN, PARTICIPANTS AND INTERVENTION

The study was initiated at 21 US trauma centers participating in the Major Extremity Research Consortium (METRC),[29] although 4 sites subsequently withdrew because of an inability to operationalize the protocol at their institution. The list of participating centers is listed at the Appendix 1. The protocol was reviewed by the Food and Drug Administration, and determined to be exempt from Investigational New Drug application requirements. Institutional Review Board (IRB) approval was obtained from the Johns Hopkins Bloomberg School of Public Health (location of the METRC Coordinating Center), the Department of Defense (DoD) Human Research Protection Office (HRPO) (study sponsor) and the local IRB at each participating center. In addition, the DoD HRPO reviewed all local IRB documents before any site engaged in research activities. Finally, the Coordinating Center reviewed all documentation and provided a final certification for participation, ensuring staff were trained on appropriate study and data collection procedures before initiation of the study.

Participants and Randomization

The study population includes patients aged 18–80 years with fractures of the proximal or distal humerus, supracondylar femur, femoral shaft, tibia plateau, tibia shaft, open ankle (with associated dislocation), tibia plafond, calcaneus, talus, or midfoot which either occur in isolation or are treated surgically as a whole and require fixation (Table 1). This group of fractures was chosen to represent a spectrum of fractures that are associated either with high rates of long-term pain and/or substantial nonunion rates. On provision of informed consent, patients are randomized in permuted blocks, which were stratified by clinical center, and varied in size across centers. The randomization scheme is a central computerized process executed through REDCap,[30] the web-based data collection system used for all METRC projects. Patients are randomized before definitive fixation and must receive at least one dose of study medications before fixation to be included in the study. Enrolled patients are followed for 12 months after injury.

Participants are enrolled in the study either within 48 hours of presenting at the participating facility or during an initial clinic visit where treatment plans are developed, but no later than 10 days after the injury. Potentially eligible participants are approached for consent in a manner consistent with the standardized METRC approach, which includes the treating surgeon or clinical site research coordinator, and material and resources for patients and family members to facilitate informed decision making about participation (see **Figure**, **Supplemental Digital Content 1**, http://links.lww.com/BOT/A871 describing the METRC consenting procedures). Patients and family members are provided an opportunity to watch a brief video that explains the treatment modalities and the randomization process. Legally authorized representatives were not permitted to consent on behalf of patients because they cannot provide information on the patient's pain experience.

Sample Size

While the overall sample sizes required to detect differences in pain intensity and morphine equivalent opioid utilization (and other proposed secondary outcome measures) are modest, larger sample sizes are required to establish noninferiority of the 2 active arms to the control arm with respect to the probability of nonunion between 6 and 12 months postsurgery. Probability of nonunion in the control arm is expected to be approximately 7% based on a combination of literature review and expert opinion from the protocol committee. We specified a noninferiority margin of 10%, so that a nonunion probability 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 comparisons, noninferiority is accepted if the upper limit of a one-sided confidence interval for the difference between the active and control probabilities of nonunion is less than 10%. To account for inflation of type I error because 2 active treatment groups are being compared with a common control group, the Dunnett procedure[31] for selecting the limits of the confidence intervals is 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 noninferiority will be less than 5%. With a sample size of 150 per treatment arm, there is a 90% chance of accepting noninferiority 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 10% missing outcome data, the sample size is increased to 165 per arm (resulting in a total of 495 participants for this study).

TABLE 1. Inclusion and Exclusion Criteria for the Pain Study

Inclusion Criteria	Exclusion Criteria
1. Patients aged 18–80 with one of the following types of injuries requiring operative treatment with fixation: Unilateral, open or closed distal and proximal humerus fractures (OTA 11A-C and OTA 13 A-C); Open femoral shaft fracture (OTA 32 A-C; Gustilo Type I-IIIC) or open or closed supracondylar femur fractures (OTA 33 A-C); Open or closed tibial plateau, shaft or pilon fractures (OTA 41,42,43A-C); Unilateral, open (type I, II, or IIIA) ankle fractures with associated dislocation on presentation (OTA 44B3 or 44C); Unilateral, Type I &II open or closed tibial plafond, calcaneus, talus fractures, and Lisfranc dislocations; Or any combination of the above injuries which are surgically treated as a whole 2. Presented to the admitting hospital acutely or clinic after an initial assessment in the emergency department, for care up to 10 days after initial injury. 3. Treating physicians agree that none of the study drugs indicated for standard of care treatment for this patient. 4. English or Spanish speaking 5. Intend to be followed at the METRC facility for at least 12 mo after injury.	1. Glasgow Coma Scale <15, loss of consciousness consistent with a clinical diagnosis of a closed head injury, or concern of a cerebrovascular hemorrhage secondary to traumatic brain injury; 2. Patient unable to provide informed consent; 3. Patients with chronic pain receiving treatment with opioid or gabapentinoid prescription or any other alternative therapy; 4. Intravenous drug abusers; 5. Other injuries (orthopaedic and other) requiring additional surgery; 6. Expected postsurgical stay <24 h; 7. Unable to swallow oral medications or without adequately functioning gastrointestinal tract; 8. History of gastrointestinal bleeds or gastric perforation; 9. History of stroke or heart attack, bleeding disorder, or severe renal failure 10. Currently receiving an aspirin or NSAID regimen (exception: low dose (81 mg) aspirin); 11. Daily treatment with systemic glucocorticoids before surgery; 12. Treatment with angiotensin-converting enzyme inhibitors; 13. Pregnant or lactating at the time of screening; 14. Severe problems maintaining follow-up.

Intervention

After consent, patients are randomly assigned to the placebo, NSAID, or gabapentin arms. All participants receive standard of care pain management in addition to the study medications. Participants enrolled for more than 24 hours before definitive fixation receive preoperative oral medication [placebo, 7.5 mg Meloxicam (Zydus, Pennington, NJ) or 75 mg Lyrica (Pfizer, New York, NY)] every 12 hours, for 14 days or until definitive fixation, whichever comes first. Participants are instructed to record pain scores and any side effects during the time they are taking these medications.

Some patients undergo intermediate procedures, such as temporary fixation or debridement, between enrollment and definitive fixation. For these patients, the preoperative oral medication is temporarily stopped, and a perioperative dosing regimen is initiated. Up to 2 hours before the procedure, participants receive a single oral dose of placebo or 300 mg Lyrica (Pfizer) and a single intravenous dose of either 50 mL normal saline or 30 mg Ketorolac (Hospira, Lake Forest, IL) in 50 mL normal saline. After fixation, participants receive oral medication (placebo or 75 mg Lyrica) every 12 hours and intravenous medication (normal saline or 30 mg Ketorolac) every 6 hours for up to 48 hours or until definitive fixation, whichever comes first. Once the 48 hours of postoperative treatment is complete, these participants return to the preoperative oral medication regimen.

The perioperative regimen for intermediate procedures is identical to that which is initiated at the time of definitive fixation, including the preoperative oral and intravenous dosing, and the 48 hours of postoperative oral and intravenous dosing. Upon completion of 48 hours of postoperative treatment, or at the time of discharge, study treatment is considered complete and the follow-up period begins.

Fisher Clinical Services is responsible for central packaging of all study medication kits. Separate kits contain (1) all doses of oral medication covering the preoperative period and (2) all oral and IV medication doses covering the perioperative period. Preoperative oral packaging is printed with a log for participants to record time/date of dosing and pain score at the time of administration. All oral medications are over-encapsulated to blind providers and patients to the treatment arm. It is not practical to manufacture sham vials of ketorolac, so only the NSAID arm perioperative kits contain these vials. Consequently, the research pharmacists who prepare the ketorolac infusions are unblinded to the study arm. However, these individuals are not involved in the care of the patient.

Protocol Changes

The protocol was amended multiple times over the course of implementation. While most of these amendments were administrative, 2 amendments were made in response to poor enrollment in the initial phases of the study. As originally proposed, the study included only isolated fractures of the calcaneus and tibia plafond, a population in which long-term pain is observed, and with a moderate rate of nonunion. However, the level I centers participating in the study saw insufficient patients with this pattern of injury who satisfied inclusion criteria to achieve the requisite sample size. Two proposed changes were made to the inclusion criteria. The first change expanded inclusion criteria to encompass a broader range of injuries to the foot and ankle, and to allow groups of fractures treated surgically as a whole to be included. A second amendment to the inclusion criteria expanded eligible injuries to include a much broader list of injuries (Table 1) that were expected to have, on average, moderate rates of nonunion regardless of likelihood of long-term pain. The investigators were comfortable in expanding the inclusion criteria because the central question that powers the study is whether the nonunion rate is affected by NSAID use, as the link between pain control and NSAID use is more firmly established, albeit not in orthopaedic trauma specifically.[12,13] A final amendment was made to prevent the enrollment of patients with a medical history of heart attack or stroke and the consent form was updated accordingly. This change in protocol was made in response to the FDA strengthening (during the study period) an existing labeling requirement warning that NSAIDS increase the chance of heart attack and stroke.

METHODS: DATA COLLECTION

Frequency and Duration of Follow-up

At baseline, information on patient demographics and injury characteristics is collected (see **Table**, **Supplemental Digital Content 1**, http://links.lww.com/BOT/A873). Throughout the time that patients receive study medications, daily pain scores (Visual Analog Scale[32]) are collected and side effects are documented by log, if the patient had gone home, or during daily rounding if the patient is still in the hospital. At 48 hours after definitive fixation, patient's pain is assessed. After discharge, patients return for study visits at 3, 6, and 12 months after injury. Study visits involve a clinical examination to evaluate ambulation status, fracture healing, incidence of any complications, including nonunion, and assignment of a modified Radiographic Union Scale in Tibia (mRUST) score[33] (when applicable). At each of these visits, patients complete an interview to assess for complications, rehospitalizations, pain, physical function, general health, and well-being. In addition, at the final 12 month interview, patients are asked about depression, PTSD, and ankle osteoarthritis.

Primary Outcomes

The primary outcomes for this study are opioid utilization during the 48 hours after definitive fixation or discharge, whichever comes first; persistent pain at 3, 6, and 12 months postinjury, as measured by the BPI[34] and the painDETECT[35] instrument for assessing neuropathic pain; and surgery for nonunion, defined as unplanned nonprophylactic surgery for nonunion performed between 6 months and 1 year after initial hospital discharge.

Secondary Outcomes

Clinical and patient-reported outcomes are collected according to the data standards adopted by the consortium.[36] The following outcomes are collected at the intervals indicated: (1) postsurgical pain intensity as measured by the Multidimensional Post-Operative Pain Scale (MPOPS),[37] the Brief Pain Inventory,[34] and the painDETECT,[35] recorded at 12-hour intervals for up to 48 hours after definitive fixation (abstracted from medical record and supplemented by participant pain logs); (2) presurgical pain intensity using the visual analog scale assessed in 12-hour intervals between study enrollment and definitive fixation surgery (abstracted from medical record and supplemented by participant pain logs); (3) adverse effects and complications, (abstracted from the medical record and from the patient logs and interviews at 3, 6, and 12 months) to include wound closure complications, bleeding complications (particularly perioperative bleeding and gastrointestinal bleeding), as well as pain treatment–related adverse effects, to 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 postoperative delirium; (4) functional outcome and general well-being measured by patient self-report at 6 and 12 months using the Short Musculoskeletal Function Assessment (SMFA)[38] and Veteran's RAND 12 Item Health Survey;[39] and (5) depressive symptoms and PTSD measured by patient self-report at 12 months using the Patient Health Questionnaire[40] and the PTSD Checklist,[41] respectively.

Medical Costs

Overall treatment costs include costs for the index hospitalization, readmission, outpatient procedures, and prescription medication for the 12 month follow-up period. Cost of hospital admission is derived using hospital bills (UB04) with charges converted to cost by applying Medicare cost-to-charge ratios. Direct medical costs for other services are estimated based on patient-reported use of specific types of encounters (eg, rehospitalizations, ambulatory surgery, emergency department visits). The cost for each encounter is estimated by applying health insurance paid claims data from a large national database (Truven MarketScan) matched on persons with similar demographics and patterns of injury.

Monitoring and Quality Assurance

Details of the METRC-wide Standard Operative Procedures for monitoring can be found in the on-line supplemental material (see **Figure**, **Supplemental Digital Content 2**, http://links.lww.com/BOT/A872). The

monitoring plan is designed to verify site compliance with the protocol, and study-specific standard operating procedures on the data collection and procedures. An independent Data Safety Monitoring Board reviews study progress, all reported complications, and all serious adverse events during meetings held twice a year. The chair of the Data Safety Monitoring Board serves as the medical monitor who reviews each serious adverse event as it is reported in real-time.

METHODS

Data Management

Data are collected by site research coordinators and clinical investigators using paper case report forms designed specifically for this study and then entered in REDCap. Details about data handling and data management can be found in the on-line supplemental material.

Data Analysis

The main statistical analyses will be conducted according to the intent-to-treat paradigm. For each outcome, separate treatment comparisons will be made between the 2 active arms and the control arm; Dunnett procedure[31] will be used to account for these multiple comparisons.

Binary Outcomes

Treatment effects for binary outcomes (eg, adverse effects, complications) will be estimated using a 2-group binomial comparison of proportions and confidence intervals for the absolute risk difference and relative risk will be reported. Tests of treatment effects will be based on both a χ^2 test and a Fisher exact test; *P* values will be reported.

Continuous Outcomes

Treatment effects for continuous end points (eg, SMFA, pain intensity) will be estimated using a 2-group comparison of means. Confidence intervals for the difference in mean values will be reported. Tests of treatment effects will be based on both a *t* test and a Wilcoxon rank-sum test and *P* values reported.

Noninferiority Analysis of Nonunions

Noninferiority will be accepted if the upper limit of a one-sided confidence interval for the difference between the active and control probabilities of nonunion is less than 10%. 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 noninferiority will be less than 5%.

We will also use statistical procedures that leverage baseline covariates to increase statistical precision (ie, power).[42] Regression modeling may be used if concerns about confounding arise, because of unexpected imbalances between treatment groups with respect to key prognostic baseline factors. Hierarchical modeling may also be used if concerns regarding the clustering of outcomes within centers emerge.

Medical Cost

Total cost of care from a payer perspective will be estimated for each treatment group and the standard of care group. Incremental cost-effectiveness for each treatment group relative to standard of care will be calculated as the ratio of difference in health care costs for each treatment group versus standard-care patients (numerator) and the between-group difference in the outcome measure of interest (denominator).[43,44] Uncertainty in the estimated differences in cost and outcome differences will be established[45,46] through the use of techniques that consider the joint density of cost and effect differences. Findings will be presented in tabular and graphical form including scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

Missing Data

Multiple imputation will be used to handle missing baseline covariates.[47–49] Missing outcomes will not be imputed. Sensitivity analyses will be conducted to evaluate the robustness of the trial results to various untestable assumptions about the missing outcome mechanism.

DISCUSSION

Considerable evidence exists that uncontrolled postoperative pain is a major risk factor for the development of chronic pain, psychosocial problems, and physical disability. This is a particular problem for military combat casualty care, as soldiers increasingly survive high-energy blasts but experience long-term pain, traumatic brain injury, and PTSD. In Clark et al's study,[26] 96% of wounded warriors reported pain-related problems during rehabilitation. In this study, the authors cited both inadequate pain control and "excessive analgesics that lead to sedation and interference with rehabilitation" as barriers. Both of these problems may be potentially addressed through multimodal pain management. Furthermore, agents such as pregabalin and meloxicam, which can be administered orally, may be powerful additions at all levels of forward care delivery, where ease of administration and frequency of side effects are key concerns. The benefit to civilian and military patients of even small reductions in pain intensity may be substantial. The use of multimodal perioperative pain management has the potential to reduce pain intensity by at least this amount and could result in improvements in both physical and psychosocial outcomes for this high-risk population.

Despite the obvious potential benefit of nonopioid medications, many orthopaedic surgeons remain hesitant to use NSAIDS in acute fracture surgery. Although development of chronic pain is a potentially life-altering occurrence, a nonunion also negatively affects patient outcomes. Many surgeons would likely trade some increase in nonunion rate for decrease in chronic pain but their willingness to accept this tradeoff would depend on the rate of each occurrence. This study will provide high-quality data on the impact of nonopioid medications on long-term pain and nonunion

rates for these fractures that will help inform decision making.

The major strength of this study is its prospective, double-blinded, placebo-controlled, randomized design. The study is being conducted in a heterogeneous population, and variability in treatment, rehabilitation timing, and length of medication exposure is expected. Although these could serve to increase the external validity of the results, they may also affect our ability to detect overall treatment effects. There is concern that follow-up, particularly for secondary outcomes measured at 6 and 12 months postinjury, may be less robust than anticipated, because of the relatively low severity of some study injuries and the possibility that participants will no longer be receiving follow-up care. Statistical techniques will be used to reduce potential biases in the reporting of results. Finally, a key limitation of the study is its inclusion of patients with only a single operative injury. Should results of this trial be favorable, a critical future research goal will be extension of the results to polytrauma patients.

It is important to note that there are currently no guidelines for the use of multimodal pharmacy for pain control in the perioperative setting. Although the use of multimodal approaches is mentioned in the current US Army Institute for Surgical Research Joint Trauma System's guidelines, no specific guidance is provided regarding the use of candidate agents, dosages, contraindications, and which patients may benefit from these approaches. As discussed above, the greatest challenge for widespread dissemination of this promising approach for the care of orthopaedic trauma patients are concerns about the possibility of complications. This study represents an important first step in establishing the evidence base that will inform these guidelines and impact care of orthopaedic trauma patients.

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APPENDIX 1. CORPORATE AUTHORS

Participating Centers: *Boston Medical Center*: Paul Tornetta III, MD, Heather Silva, BS, and Hope Carlisle, RN, BSN; *Carolinas Medical Center*: Michael J. Bosse MD, Christine Churchill, MA, Joseph R. Hsu, MD, Madhav A. Karunakar, MD, Rachel B. Seymour, PhD, and Stephen H. Sims, MD; *The CORE Institute, MORE Foundation*: Clifford B. Jones, MD; Debra L. Sietsema, PhD; *Eskenazi Health*: Jeffrey O. Anglen, MD, Janos P. Ertl, MD, Brian H. Mullis, MD, and Karl D. Shively, MD; *Hennepin County Medical Center*: Andrew H. Schmidt, MD, Gudrun E. Mirick, MD, and Jerald R. Westberg, BA; *Louisiana State University Health Sciences Center Shreveport*: Todd Jaeblon, DO and Massimo 'Max' Morandi, MD, FACS; *MetroHealth Medical Center*: Heather A. Vallier MD; *Methodist Hospital*: Janos P. Ertl, MD, Brian H. Mullis, MD, Karl D. Shively, MD; *Naval Medical Center Portsmouth*: LCDR Christopher S. Smith, MD and Colin V. Crickard, MD; *University of Maryland R Adams Cowley Shock Trauma Center*: Robert V. O'Toole, MD, Daniel Connelly, BS, Timothy G. Costales, MD, Yasmin Degani, MPH, Dimitrius P. Marinos, BS, Daniel C. Mascarenhas, BS, George B. Reahl, BS, and Gerard P. Slobogean, MD, MPH; *University of Miami Ryder Trauma Center*: Gabriela M. Zych, BS, CCRC and Gregory A. Zych, DO; *The University of Texas Health Science Center at Houston*: Joshua L. Gary, MD, Kathy Franco BSN, CCRC, Matthew C. Galpin, CCRC, William H. Harvin, MD, and Jaideep Mehta, MD, MBA; *University of Iowa Hospitals and Clinics*: Michael Willey, MD; *University of Pittsburgh*: Ivan S. Tarkin, MD; *University of Texas Southwestern Medical Center*: Ashoke K. Sathy, MD and Cindy G. Daniel, CCRP; *Vanderbilt Medical Center*: William T. Obremskey, MD, MPH, MMHC, Kristin R. Archer, PhD, DPT, Robert H. Boyce, MD, Andres Rodriguez Buitrago, MD, Eduardo Burgos, MD, Vamshi Gajari MD, A. Alex Jahangir MD, MMHC, Hassan R. Mir, MD, MBA (now at University of South Florida Department of Orthopaedic Surgery), Manish K. Sethi, MD, and Rajesh R. Tummuru, MBBS. **Other Corporate Authors**: *Johns Hopkins School of Medicine*: Srinivasa N. Raja, MBBS, MD (co-principal investigator), Allan Gottschalk, MD, PhD (protocol committee member), and Stephen T. Wegener, PhD (protocol committee member); *Brooke Army Medical Center*: Brendan Goff, DO (protocol committee member); **METRC Coordinating Center at Johns Hopkins Bloomberg School of Public Health:** Renan C. Castillo, PhD, Lauren E. Allen, MA, Anthony R. Carlini, MS, Gregory de Lissovoy, PhD, Katherine P. Frey, RN, MPH, Ellen J. MacKenzie, PhD, Daniel O. Scharfstein, ScD, Tara J. Taylor, MPH, and Yingjie Weng, MHS.