A Three-Arm, Double-Blinded, Randomized Controlled Trial Comparing the Efficacy of Adductor Canal Pain Catheters Following Total Knee Arthroplasty

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
TKA	Total Knee Arthroplasty
OME	Oral Morphine Equivalents

Study Summary

Title	A Three-Arm, Double-Blinded, Randomized Controlled Trial Comparing the Efficacy of Adductor Canal Pain Catheters following Total Knee Arthroplasty
Running Title	Adductor Catheter Efficacy Following Total Knee Arthroplasty
Protocol Number	Pending
Phase	Phase III
Methodology	Double-Blinded Randomized Controlled Trial
Overall Study Duration	12 months
Subject Participation Duration	60 days, or until discontinuation of narcotic medication (whichever is later)
Single or Multi-Site	Single Center
Objectives	● Aim 1 will be to compare postoperative pain levels between groups ● Aim 2 will be to compare use of the patient-administered dosing between groups ● Aim 3 will be to compare duration of narcotic use between groups
Number of Subjects	84
Diagnosis and Main Inclusion Criteria	Narcotic naïve patients who have a diagnosis of osteoarthritis and are undergoing a primary total knee arthroplasty are eligible for the study.
Study Product, Dose, Route, Regimen	This study will evaluate the efficacy of adductor canal pain catheters following total knee arthroplasty, using either an intermittent bolus or continuous infusion compared to a single-shot adductor canal block.
Duration of Administration	4 days
Reference therapy	Single-shot adductor canal block
Statistical Methodology	Statistical analysis will be performed on the basis of the intention to treat principle. Comparisons between treatment groups will be made using Wilcoxon rank sum test or Fisher's exact test.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

There has been a rapid rise in opioid consumption and deaths in the United States (US) due to opioid use and abuse. In 2017 the Center for Disease Control (CDC) estimated that 72,000 deaths were related to drug overdose, with a large proportion of these stemming from prescription medications. This rate was an approximate two-fold increase over the previous decade and does not include an additional 2 million who are estimated to suffer from a substance abuse disorder related to opioid medications.[1,2] The high rate of opioid over-prescription following surgery is thought to contribute to the current epidemic.[3] In 2014 the National Survey on Drug Use and Health estimated that more than 10 million people in the United States used opioids outside of their prescribed intent, and that 55% of the medication was obtained from a friend or relative.[4] Therefore, mitigating the amount of narcotics available for diversion is particularly important in order to help combat the opioid crisis.

Orthopedic surgeons are the third highest opioid prescribers (*Combatting Opioid Misuse. 2017. https://www.aaos.org/AAOSNow/2017/Jun/YourAAOS/youraaos10/?ssopc=1*). Previous work demonstrated that surgeons prescribe three times the narcotics required by the patient and that most patients do not properly dispose of leftover medication.[5-8] Additionally, in a separate study, 13% of narcotic naïve patients became prolonged opioid users following elective orthopedic procedures.[9] There is a *critical need* to find alternative approaches to postoperative pain management that rely less on narcotic medication.

We previously reported on risk factors for patients requiring additional opioid prescriptions following surgery and have demonstrated that a collaborative approach between the anesthesia and orthopedic teams, utilizing both local and regional nerve blocks, reduced pain scores with a simultaneous 43% decrease in oral morphine equivalents consumed during the hospitalization.[10,11] Additional studies have focused on multimodal pain regimens, but have not evaluated the efficacy of these regimens with adductor pain catheters.[12-17] We recently performed a randomized, prospective, double-blinded, placebo-controlled trial using a multimodal regimen with and without schedule II opioids following total knee arthroplasty. In that study we utilized an adductor canal pain catheter with a continuous infusion for four days postoperatively. We demonstrated equivalent postoperative pain scores in the oxycodone and placebo group with use of the adductor catheter. However, despite these similar pain scores, 20% of the oxycodone cohort required continued narcotic medication at 60 days postoperatively (*submitted for publication*).

It is currently unknown if a continuous infusion is the most efficacious form of medication delivery through the catheter. Recent studies have begun to evaluate intermittent bolus infusions, with the belief that catheter placement is less critical when compared to a continuous infusion.

Our study is intended to directly compare these delivery modes in a double-blinded, randomized controlled trial.

1.2 Investigational Agent

This study is not evaluating a specific drug, but rather the safety and efficacy of delivery modes for an adductor canal pain catheter following total knee arthroplasty.

1.3 Clinical Data to Date

Research has focused on prescribing practices, demonstrating the risks of long-term opioid use with large initial prescriptions.[5,8,20] This has led hospitals to develop institutional guidelines to reduce excessive prescriptions of narcotics following routine surgical procedures. For example, Wyles et al. demonstrated a reduction in the average oral morphine equivalents (OMEs) prescribed at discharge from 750 to 388 following total joint arthroplasty, after departmental adoption of standard prescribing guidelines. Interestingly, the authors reported no increase in refill rates, suggesting that the change largely reduced the amount of unused medication.[21]

At our own center we reported that the number of OMEs prescribed at discharge was not predictive of patients requesting a refill of their medication. We instead found that patients with lower pain scores on postoperative day #1, but not postoperative day #2, had a lower risk of requiring a refill of their pain medication.[11] We hypothesized that patients who developed an early reliance on narcotics would be harder to wean from the medication and be at a greater risk of long-term opioid use. Due to this we began to utilize an adductor canal pain catheter for total knee arthroplasty patients to provide improved pain control early in the postoperative period. Following adoption of the adductor canal catheter we reported a subsequent 43% decrease with in-hospital narcotic use.[10] Building upon this we then completed a prospective, randomized, double-blinded, placebo-controlled trial comparing our multimodal regimen with and without schedule II narcotics (oxycodone). In that study we demonstrated equivalent pain scores between the narcotic and placebo group when using a continuous infusion adductor canal pain catheter. The narcotic group, however, had a higher proportion of patients that required pain medication at 60 days postoperatively (*submitted for publication*).

Our goal is to expand upon our previous work and evaluate the safety and efficacy of differing modes of medication delivery with the adductor catheter in order to further optimize postoperative pain control (***Aim 1***). It is hypothesized that intermittent bolus infusions of the medication will provide improved pain control when compared to a continuous infusion due to the ability to more completely saturate the surrounding anatomy in cases where the catheter is not placed in the optimal location adjacent to the nerve. We additionally intend to compare the use of patient-administered dosing (***Aim 2***) and overall duration of narcotic use between cohorts (***Aim 3***).

1.4 Dose Rationale

The dosing of the medications are all currently used following joint replacement procedures.

1.5 Risks and Benefits

The benefits of the study will be to evaluate the efficacy of the differing modes of medication delivery through the adductor canal pain catheter. If optimized, we believe this will allow us to continue to reduce the amount of narcotic medications prescribed following orthopedic surgery.

All components of the multimodal pain regimen are currently safely used in orthopedic patients. There is a theoretical risk of renal damage or GI upset with the use of anti-inflammatory medications, but we have not seen this with our total knee study. There is also the possibility that patients will have uncontrolled pain following surgery. These patients will have IV narcotic medication as a safety net during their hospitalization and will be able to utilize our standard opioid regimen upon discharge.

2 Study Objectives

Primary Objective

The primary objective will be to compare postoperative pain levels between the treatment groups, using the Numerical Rating Scale (NRS).

Secondary Objective

The secondary objectives will be to compare the amount of patient-administered medication use between groups as well as duration of narcotic use between groups.

3 Study Design

This project will be conducted as a three-arm double-blinded, randomized controlled trial comparing differing modes of medication dispersion using the adductor canal pain catheters. The three arms will be a single shot adductor canal block (with saline filled catheter) compared to ropivacaine 0.2% continuous infusion, and ropivacaine 0.2% intermittent bolus infusions. Treatment groups will be assigned to patients using computer-based randomization via the dynamic allocation method of Pocock and Simon. Subjects will be screened in the outpatient clinic setting and those interested and eligible will be consented and enrolled in the trial.

A total of 84 patients will be enrolled in this study. Twenty eight patients will be in each comparison group. After enrollment patients will undergo randomization by the research pharmacy in order to maintain blinding of the surgical team, nursing staff, and patient. The patient will then undergo their surgical procedure and receive a multi-modal pain regimen as described below. All treatment groups will receive the same regimen with the exception of the adductor canal catheter. All of the patients will have the catheter placed in the Post Anesthesia Care Unit following

surgery and bolused with 10 mL of 0.5% ropivacaine. The pumps will be loaded with saline (single shot adductor canal group), or ropivacaine 0.2%, dispersed in either a continuous infusion (6 mL/hr) or pulsed intermittent bolus (8 mL every 2 hours). All groups will have a patient demand dose of 6 mL/hr for anterior knee pain. The medication for the adductor catheter will be dispersed to the anesthesia team by the research pharmacy. The anesthesia team will place the catheter under ultrasound guidance in the recovery room. They will adjust the delivery mode based on patient randomization. The anesthesia team will record the serial number of the pump at the time of placement.

Questionnaires will be sent electronically to the patient. Results will be collected daily for 14 days postoperatively, followed by weekly questionnaires until they discontinue narcotic medications. Additional questionnaires will be collected at 30 and 60 days postoperatively in order to record pain and KOOS Jr. scores. The questionnaires will be sent in the morning; if a patient fails to fill out the questionnaire by the afternoon, a member of the research team will contact the patient to obtain the data. The questionnaires will document numerical rating scale (NRS) pain scores, information on symptoms of nausea, vomiting, and constipation, and will inquire if the patient is still consuming narcotic medication.

Following discontinuation of the catheter the patient will remove and return the device to the supplier. The supplier will then provide the rate of on-demand usage to the research team by way of device serial number. This information will be stored in Redcap.

Subjects will be withdrawn prior to completion if they ask to be removed from the study. They may also be withdrawn from the study if they have a serious adverse reaction to one of the prescribed medications. Finally, subjects may be withdrawn at the discretion of the treating physician. If subjects are withdrawn early their last recorded pain score will be carried forward until study conclusion in order to perform intention to treat analysis. The study will continue to ascertain duration of narcotic use with weekly questionnaires, until the patient has stopped the medication.

3.1 General Description

Patients will receive the following multi-modal pain regimen in addition to the adductor canal pain catheter.

Preoperative (All patients receive the following in the pre-op holding):
Acetaminophen 1000 mg oral
Celebrex 400 mg oral
Dexamethasone 10 mg IV

Intraoperative (All patients receive the following):
Periarticular block

- Ketorolac 30 mg with weight-based ropivacaine and epinephrine, diluted in normal saline to a total volume of 120 mL (50-74.9 kg – ropivacaine 200 mg, epinephrine 0.1 mg), (75 – 99.9 kg – ropivacaine 300 mg, epinephrine 0.2 mg), (100 kg and greater – ropivacaine 400 mg , epinephrine 0.3 mg).

Postoperative:
Adductor canal pain catheter (saline or ropivacaine)
Acetaminophen 1000 mg oral every 6 hours scheduled
Tramadol 50 mg oral every 6 hours as needed
Dexamethasone 10 mg IV scheduled daily while hospitalized (*max 3 days*)
Toradol 10 mg oral every 6 hours scheduled daily while hospitalized (*max 3 days*)
Oxycodone 5 mg every 3 hours as needed for pain
Dilaudid 0.5 mg IV push every 3 hours as needed for pain > 8 on VAS score

Discharge:
Acetaminophen 1000 mg oral every 6 hours scheduled (x2 weeks)
Tramadol 50 mg oral every 6 hours as needed for pain
Celebrex 400 mg oral scheduled daily (x2 weeks)
Oxycodone 5 mg every 3 hours as needed for pain

At the time of discharge, medications will be filled for two weeks. Patients will report their pain scores during this time via electronic and phone surveys. If additional pain medications are required these will be filled per the treating physician's discretion.

3.2 Number of Subjects

Twenty eight patients will be recruited into each arm, for a total of 84 patients. This will serve as a pilot study to determine feasibility.

3.3 Duration of Participation

Results will be collected daily for 14 days postoperatively, followed by weekly questionnaires until patients discontinue narcotic medication. Additional questionnaires will be collected at 30 and 60 days postoperatively in order to record pain and KOOS Jr. scores.

3.4 Primary Study Endpoints

The primary endpoint will be pain scores, calculated by the Numerical Rating Scale. This score will be collected daily during the hospital examination and by online or phone surveys after discharge. We will calculate the mean difference in recorded pain scores between cohorts. We hypothesize that the intermittent bolus infusion cohort will report improved pain scores compared to continuous infusion catheters.

3.5 Secondary Study Endpoints

The secondary endpoints will be the amount of medication administered via the patient-controlled function on the adductor catheter as well as duration of narcotic use required in each cohort. We hypothesize that the intermittent bolus cohort will require fewer doses of patient-administered medication and will use narcotic medication for a shorter duration when compared to the continuous infusion and placebo groups.

We will additionally calculate the overall morphine equivalents used in each cohort during their hospitalization, and dividing this by the total number of post-surgical hospitalization hours in order to normalize the data.

Nausea and vomiting will be recorded daily using the postoperative nausea and vomiting scale and compared between groups. Presence of constipation will be a subjective rating by the patient that is also recorded daily. We will compare the post-surgery length of hospitalization between groups. Finally, we will compare patient-reported outcomes using the KOOS Jr. questionnaire.

We hypothesize that the intermittent bolus cohort will use less narcotic mediation and will therefore have lower rates of constipation, nausea and vomiting. Furthermore, we believe this cohort will demonstrate equivalent lengths of stay and patient-reported outcomes as compared to the comparison groups.

3.6 Primary Safety Endpoints

If patients report serious adverse side effects from a medication in the multi-modal regimen, or if they report uncontrolled pain, they will be withdrawn from the study and provided alternative medication per the treating surgeon's discretion.

3.7 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF) at the pre-op visit and inputted into REDcap, a password protected database.

- Name
- Medical Record Number
- Email address
- Date of Birth, Age
- Gender
- Race
- Weight (lbs), Height (In), BMI
- Previous surgeries? (yes, no)
- Are you taking Nsaids? (yes, no)
- Previous injections (yes, no)
- Baseline NRS score
- Laterality of surgery
- KOOS Jr. Questionnaire
- Device serial number

The following source data will be recorded daily for two weeks using an online questionnaire recorded into REDcap, and continued weekly until discontinuation of narcotic medication. This data will again be collected at 30 and 60 days following the date of surgery.

- Name
- Medical Record Number
- Date of Birth
- How long has it been since your operation? (Less than 1 month, 1-2 months, Greater than 2 months)
- Are you using narcotic medication? (yes/no)
    - What was the date you last consumed narcotic medication? (if no to previous answer)
- How would you rate the pain you have been experiencing? (0-10)

- Have you been experiencing constipation over the past 24 hours? (yes, no)
- Have you been vomiting or had dry-retching over the past 24 hours? (once, twice, three or more times, no)
- Have you been experiencing a feeling of nausea (an unsettled feeling in the stomach and slight urge to vomit) over the past 24 hours? (yes, no)
- KOOS Jr. Questionnaire (only recorded during 1 month and 2 month questionnaires)
- Rate of on-demand catheter use (recorded at final survey only)

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Age $\geq$ 18 and < 90 years.
2. Willing to participate in the study and competent to provide informed consent.
3. Willing to comply with protocol procedures.
4. Has an underlying diagnosis of osteoarthritis indicated for a total knee arthroplasty.

4.2 Exclusion Criteria

1. The patient must not have taken a schedule II narcotic daily, for 7 consecutive days, during the 3 months leading up to the surgery
2. The patient must not be allergic or intolerant to a medication used in the multimodal pain pathway
3. Revision knee arthroplasty
4. Uncontrolled diabetes with A1C > 8.0 %
5. Pregnant patients

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be identified and enrolled from the principal investigator and co-investigator's clinical practices. If the patients are eligible for the study and wish to participate then they will be enrolled.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects will be withdrawn from the study prior to completion if they ask to be removed from the study. They will also be withdrawn if they do not complete the protocol requirements or have a serious adverse reaction to one of the medications in the multi-modal regimen. Finally, subjects may be withdrawn from the study at the discretion of the treating physician.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If subjects are withdrawn from the study prior to completion we will collect the data prior to withdrawal. At the conclusion of the study we will note the number of subjects that were withdrawn from the study as well as the reasons for withdrawal.

5 Study Drug

5.1 Description

See section 3.1 for the multi-modal pain regimen that will be used.

5.2 Treatment Regimen

See section 3.1 for the multi-modal pain regimen that will be used.

5.3 Method for Assigning Subjects to Treatment Groups

Patients will undergo computer randomization by the research pharmacy prior to dispensing the medication in order to ensure that the treating physician (surgeon) remains blinded to the study.

5.4 Preparation and Administration of Study Drug

The medication that will be loaded in the adductor catheter will be dispensed by the research pharmacy to the anesthesia team to ensure blinding of the surgical team.

5.5 Subject Compliance Monitoring

Patient compliance during the hospitalization will be tracked by the surgical team. Following discharge patients will be contacted daily for 2 weeks, followed by weekly questionnaires until they have discontinued all narcotic medication.

5.6 Prior and Concomitant Therapy

If a patient has taken a narcotic medication (schedule II) in the 3 months leading up to surgery they will be excluded from the study. Patients may request and be provided refills for narcotic medication at the discretion of the treating surgeon.

5.7 Packaging

The medication will be provided by the research pharmacy and dispensed to the anesthesia team for loading into the adductor canal pain catheter. This will be secured until the medication is fully dispensed.

5.8 Masking/Blinding of Study

This will be a double-blinded study. Computer randomization will be used for patient grouping and the research pharmacy will dispense the medication to the anesthesia team, who will set the adductor catheter dosing based upon randomization. The surgical team and patient will remain blinded to the medication and dosing regimen.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Not applicable

5.9.2 Storage

Once dispensed to the anesthesia team, the medication will be loaded into the adductor canal catheter, which will be secured until the medication is fully dispensed.

5.9.3 Dispensing of Study Drug

The adductor catheter settings (continuous versus intermittent bolus infusions) will be selected by the anesthesia team, based upon patient randomization. This information will be provided to the anesthesia team by the research pharmacy in order to maintain blinding of the surgical team.

5.9.4 Return or Destruction of Study Drug

After the medication has been fully dispensed (postoperative day #4), patients will remove the adductor catheter and send the pump to Avanos for processing.

6 Study Procedures

6.1 Visit 1

At visit #1 patients will be screened for eligibility for inclusion in the study. If agreeable, an informed consent will be signed.

6.2 Visit 2

Patients will undergo standard preoperative clearance testing.

6.3 Visit 3

Patients will then proceed with the total knee replacement procedure. During the hospitalization we will record daily pain, nausea, vomiting, and constipation levels. Following the hospitalization these values will continue to be recorded daily utilizing an online questionnaire. If patients fail to complete the questionnaire then we will contact the patient via phone to record the daily value.

6.4 Visit 4

At 2 weeks the patients will return for a standard postoperative visit. The patient will then receive an online questionnaire weekly until they discontinue narcotic medication. They will receive additional surveys at 30 and 60 days following surgery.

7 Statistical Plan

7.1 Sample Size Determination

Twenty eight patients will be recruited into each arm, for a total of 84 patients. This number has been chosen for feasibility rather than based on a formal power analysis. We will use this study to provide data for a formal power analysis in order to power a larger study.

7.2 Statistical Methods

Descriptive and Inferential Statistics

Continuous variables will be summarized with the sample mean, median, standard deviation, minimum, 25th percentile, 75th percentile, and maximum. Categorical variables will be summarized with number and percentage of patients. All analysis will be performed on the basis of the intention-to-treat principle. Comparisons of endpoints between the three treatment arms will be made using a Wilcoxon rank sum test (continuous or ordinal endpoints) or Fisher's exact test (categorical endpoints). Missing data will be imputed using either the last observation carried forward method, a regression-based approach, or another method, depending on the extent of missing data. In order to adjust for the three pair-wise comparisons between treatment groups that will be made for each endpoint, we will utilize a Bonferroni correction for multiple testing, after which p-values of < 0.0167 will be considered as statistically significant. All statistical tests will be two-sided.

Primary Hypothesis:

We hypothesize that the intermittent bolus infusion cohort will report improved pain scores compared to continuous infusion catheters and placebo cohorts.

Secondary Hypothesis:

We hypothesize that the intermittent bolus cohort will require fewer doses of patient-administered medication and will use narcotic medication for a shorter duration when compared to the continuous infusion and placebo groups.

Interim Analysis

We will evaluate the first twenty patients. If 50% of the patients are withdrawn from the study for poor pain control or serious adverse reactions to the study medication, then we will close the study early.

7.3 Subject Population(s) for Analysis

All patients who completed the study will be included in the final analysis. Additionally, we will note patient withdrawal rates as well as the reasons for patient withdrawal.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study the follow-up period is defined as 2 weeks following the surgical procedure.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if the post-treatment liver or renal function labs demonstrate a significant elevation from the recorded baseline value.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances: Elective surgical procedures.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

Not applicable.

8.4 Unmasking/Unblinding Procedures

If patients are withdrawn early from the study they will be unblinded at that time.

8.5 Stopping Rules

Subjects will be withdrawn from the study if they have a serious adverse reaction to any of the study drugs. Additionally, if patients are unable to complete the follow-up questionnaires they will be withdrawn. If patient's pain increases during the study period that is not tolerable without additional narcotic medication they will be withdrawn. Finally, we will withdraw patients from the study that no longer wish to participate.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

Subject Safety
Specific subject safety parameters include the following information: For the first twenty patients in the study, patients will return to the clinic at the two-week postoperative appointment. Documentation will include levels of pain at the site and any other concerns expressed by the patient. The patients will be assessed for any adverse reaction. This data will be submitted to the sponsor for review and the study will continue enrolling additional patients. Adverse events which would result in possible termination of the study include death, life-threatening adverse experience, patient hospitalization due to drug effects, disability and/or incapacity.

For patients #21 through #84, the subject will be instructed to call the orthopedic department to report any concerns. If the patient has any concerns about a potential adverse reaction, the patient will be promptly seen in the orthopedic clinic.

Data Integrity
Data elements to be reviewed include subject inclusion criteria being met and that the transcription of data is accurate and complete. Data elements will be reviewed at a minimum of every 20 patients being collected by the research coordinator and principal investigator.

Subject Privacy

Consenting will take place in the orthopedic department. They will be informed of the study and given the opportunity to be consented to participate. Consent to participate in the study will only be attempted once.

Data Confidentiality

Hard copy data such as consent forms will be stored in locked file cabinets; electronic data will be stored in our secure web-based database (REDCap) that will be designed with the help of the statistician.

Product Accountability
All portions of the multimodal regimen are commercially available.

Study Documentation
Study file management system as directed by the Study File Management Checklists for FDA-Regulated Studies will be utilized where applicable.

Study Coordination
Debriefing will be performed after the first 20 patients to determine if expectations are clear and if educational needs exist. Scheduled meetings will be sent out via departmental email, and meeting outcomes are noted and available to staff.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If

the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Data will be verified by the investigator after each subject visit, then entered into REDcap database.

Data Processing

REDcap data will be exported into statistical software and analyzed.

Data Security and Confidentiality

All data will be stored on password and access protected shared drives. These drives contain archives with audit trails indicating the date, time, and person ID when the data is accessed. The patient information will be de-identified through the use of study IDs.

Data Quality Assurance

Data quality is checked during the archiving and organization process. Paper data is reviewed prior to scanning and e-filing.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports as outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"

[redacted]

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

Pending

12.2 Conflict of Interest

None of the investigators claim any relevant conflicts of interest in this study.

13 Publication Plan

We have no publication policy requirements for this study.

14 References

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