Title: **Are Opioids Needed? A Double-Blinded, Randomized Controlled Trial and Examination of Predictors of Opioid Use Following ACL Reconstruction**

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Emory IRB Biomedical Protocol Outline
For Investigator-Initiated Studies

1. **Title Page**:

   Are Opioids Needed? A Double-Blinded, Randomized Controlled Trial and Examination of Predictors of Opioid Use Following ACL Reconstruction

   Short title: Are Opioids Needed?

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   Sponsor: Orthopaedic Research and Education Foundation

   Protocol version number and version date: Version 7; 04/04/2022

2. External (non-Emory) Collaborators (if applicable): n/a

3. **Precis/Abstract**:

As the public health sector continues to confront the opioid epidemic, orthopaedic surgeons must revisit pain management protocols to reduce unnecessary opioid prescriptions. The long-term goal is to reduce opioid use and residual opioids in circulation. The purposes are to 1) conduct a double-blinded randomized controlled trial to determine the effectiveness of opioid versus non-opioid medications on post-surgical pain, and 2) examine predictors of opioid usage in individuals following ACL reconstruction. Patients will use an innovative Smartphone application to track pain and medication usage. Additionally, patients will complete quality of life and pain catastrophizing questionnaires, as well as undergo pain threshold testing, to be used in a model to determine predictors of greater post-surgical opioid use. This study will provide information on non-opioid alternatives and specific predictors of post-surgical opioid use that can be used to develop prescribing protocols. These findings will help orthopaedic surgeons make informed decisions when tailoring individualized prescriptions for patients following ACL reconstruction. Importantly, findings will be readily translatable into research to reduce opioid use in other orthopaedic surgical cohorts as well. Our ultimate goal is to lessen the burden of the opioid epidemic on not only our orthopaedic patients, but also society, by minimizing the number of opioids left in circulation.

4. **Introduction and Background**:

The opioid epidemic continues to cause great morbidity and mortality across the United States. An estimated 2.4 million people in the US meet the criteria for severe opioid use disorder.[13] Since 2013, opioid overdose-related deaths have surpassed death counts from motor vehicle accidents,[10] making opioid overuse the largest single cause of preventable death. Of all of the medical specialties, orthopaedic surgery is commonly implicated as a contributor to opioid over-prescription, and orthopaedic surgeons are ranked third highest prescribers among physicians in the US.[6] As the public health sector continues to confront the massive opioid epidemic, orthopaedic surgeons must revisit post-operative pain management protocols in addressing the critical need to reduce unnecessary and potentially irresponsible opioid prescription use.

Our long-term goal is to reduce opioid use and residual opioids in circulation, while maximizing pain management for patients undergoing orthopaedic procedures. As a first step toward achieving this goal, we will focus on ACL reconstruction, which affects 200,000 people annually in the US. Given the young age of individuals undergoing ACL reconstruction, this is often their first exposure to opioid medications. As an estimated 2.1 million people misuse prescription opioids during their first exposure, these ACL patients are at major risk of prescription misuse. Currently, there is no consensus regarding the optimal dosing regimen.

Our team has generated compelling data on opioid use patterns following ACL reconstruction.[3] A series of 264 patients were prescribed varied quantities of opioids (50 tablets vs 30 tablets). Alarmingly, a large number of opioids remained unused in both cohorts, demonstrating how easily excess opioids can remain in circulation. Additionally, the following major takeaways were learned: 1) patients adjusted their opioid use based on number of tablets originally prescribed; 2) patients used opioids for less days and reported less side effects when prescribed less; and 3) patients reported similar pain levels. (Table 1) Most interestingly, 16% of patients did not use opioids at all.

Table 1. Preliminary Data

	50-Tablet	30-Tablet	*p*-value
Narcotic Tablets Taken	25.4 ± 13.8	15.6 ± 8.5	**<0.001**
Tablets Remaining	24.6 ± 13.8	14.4 ± 8.5	**<0.001**
Days of Opioid Use	5.8 ± 4.6	4.5 ± 2.9	**0.034**
Pain Score (Day 6)	2.2 ± 1.7	2.7 ± 1.4	0.466

These data come in support of our **central hypothesis** which posits that **opioid use is not solely dependent on pain,** and that other contributing factors, such as quality of life and pain catastrophizing (i.e., fear of pain), may be involved in the amount of opioids patients use. To test this hypothesis and build on preliminary data, we propose to conduct a double-blind, randomized controlled clinical trial, in which patients undergoing ACL reconstruction will be randomized to receive opioid (oxycodone) or non-opioid (acetaminophen) prescriptions for post-surgical pain (Aim 1). Patients will use our innovative Smartphone application developed in our department to monitor pain levels, medication usage, sleep, and side effects. To further understand this complex relationship between pain and opioid use, we will study other predictors of post-surgical medication usage (i.e., quality of life).

5. **Objectives**:

Aim 1: To compare the effectiveness of opioid versus non-opioid medication use following ACL reconstruction.

Hypothesis 1: Patients receiving non-opioid pain medications will have non-inferior pain scores (i.e., numeric pain scale rating scores that are less than, or equal to, to that of the patients receiving opioids).

Hypothesis 2: Patients receiving non-opioid pain medications will demonstrate a significantly decreased use of pain medications and reported side effects compared to those receiving opioid pain medications.

Aim 2: To examine predictors of pain and medication usage in individuals following ACL reconstruction.

Hypotheses: We hypothesize that greater pre-surgical pain catastrophizing levels, decreased quality of life, and decreased pain threshold measures will be predictive of greater post-surgical opioid use.

6. **Study design and methods**:

Aim 1 is a prospective randomized controlled trial of 100 patients undergoing ACL reconstruction with the PI. It is important to note that aside from the randomization to receive opioids versus no opioids (with rescue medications), all procedures are already standard of care. Regardless, we will obtain full consent and HIPPA authorization from patients (and parents/guardians if <18 years).

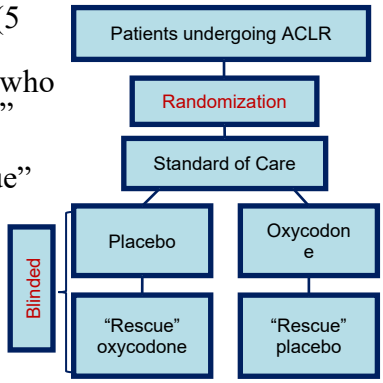
Aim 2 is a prospective study of consecutive patients of PI undergoing ACL reconstruction. This aim is entirely covered by standard of care. For this reason, in addition to the large proposed sample size in Aim 2 (n=200), we are requesting oral consent/assent process.

AIM 1

Design: Aim 1 will be a double-blind, randomized controlled clinical trial in patients undergoing ACL reconstruction. (**Figure 1**) All patients will receive the following as part of standard of care:

1. Oral non-opioid (1000 mg acetaminophen), every 8 hours.
2. Prescription of non-opioid non-steroidal anti-inflammatory medication (naproxen 500 mg) to be used 2x/day post-surgery.
3. Standardized multimodal intra- and post-operative protocols, including an adductor canal peripheral nerve block.
4. Intraoperative education on post-surgical pain management. This includes encouragement, regardless of group allocation, to not use opioids, if not needed (pain levels <7 on Numeric Rating Scale). (We tell our patients to consider using the opioid medication if intense pain prevents watching their favorite show, enjoying their meals, talking with friend, etc.)

Figure 1



Patients will be randomized to receive opioid tablets versus placebo tablets. Those patients in this opioid group will receive 15 oral opioid tablets (5 mg oxycodone) and those in placebo group will receive 15 placebo tablets. All patients will also receive 8 "rescue" medications: Patients who randomize to the non-opioid arm will receive 5mg oxycodone "rescue" tablets, while patients who randomize to the opioid arm will be given placebo "rescue" medications. The oxycodone arm will receive "rescue" placebo tablets to ensure consistency between groups. Importantly, the total number of tablets in either group is far less than the number of tablets that was prescribed (first 50 tablets, then 30 tablets) in our early studies.[3] Placebo tablets (both trial and "rescue") will be matched to size, shape, color, and texture of oxycodone tablets. These "rescue" medications are to be used only if pain is >8 (on Numeric Rating Scale 1-10) and does not improve within 4 hours of taking prior pain medication.

Safety: We can justify these procedures because of the following information and safety procedures:

- Information from our pilot studies and the literature:
  - No patients in our reduced dosage pilot study required medication beyond the 5 mg oxycodone every 4-6 hours.
  - Our preliminary data show that few patients need opioids 4-5 days after surgery (Table 1).
  - Opioids are currently not the post-operative standard of care for ACL surgery in Japan, Germany, Italy, and many other countries.
  - Also, this method of "rescue" medication has been successfully used in a recent randomized controlled trial in shoulder arthroscopy, presented by Thompson et al. at the 2019 AOSSM conference.
- Safety procedures:
  - As standard of care, all patients will also stay well under the recommended daily maximum for acetaminophen (4000mg per 24 hrs [fda.gov]).

- All patients will be provided a telephone number that is the direct line to the physician's clinical assistant. Patients can call this number to speak with the clinical assistant about their pain management questions. This staff member will contact the PI, if needed. At this point, if safety is a concern or an alternative pain management plan is needed, the orthopaedic surgeon will be unblinded to treat patient appropriately.
- Additionally, patients will be contacted post-surgery by the clinical assistant to review patient concerns.
- All patients will attend their standard-of-care post-operative visit on Day 3 or 4 post-surgery, where satisfaction with pain management will be discussed. The clinical assistant will record if patients used any "rescue" medications.
- If safety is a concern or an alternative pain management plan is needed, the orthopaedic surgeon will be unblinded to treat patients appropriately. All events requiring unblinding, as well as any adverse events, will be recorded and documented. All study staff will be notified of these events, and appropriate reporting procedures will be followed.

For leftover opioid disposal, we will follow the standard of care in our department, in which all patients are educated on proper disposal practices. These practices involve following FDA recommendations to bring extra opioids to a local take-back location or to flush extra opioids down the toilet. (Oxycodone is on FDA "flush list.") Patients will also have the option to bring in their leftover opioid medications to be properly disposed of by study team.

Recruitment: Patients scheduled to undergo ACL reconstruction at ambulatory surgery center will be recruited by clinical research staff. Upon meeting inclusion criteria and provision of consent, patients will be prospectively enrolled.

Randomization sequence will be created using SAS 9.4 (SAS Institute Inc., Cary, NC) statistical software with a 1:1 allocation using random block sizes of 2, 4, and 6. Non-study personnel will prepare the allocation sequence and conceal it from the orthopaedic surgeon in sequentially numbered, sealed, and opaque envelopes. On the day of surgery, only after all enrollment procedures have been completed, the non-study personnel will select the next sealed envelope, write patient name on it, and then open the envelope, which will randomize the patient. Envelopes with patient information will be stored in a locked cabinet and will not be revealed to ortho surgeon (PI) during data collection. Notes will be made on patient charts requesting that medical personnel do not reveal group allocation to patients.

Blinding: This study will be double-blinded. Both participants and PI (orthopaedic surgeon) will be blinded. Placebo pills will be closely matched to oxycodone pills, so patients will not know to which group they are allocated. The PI will be blinded to group allocation. In order to keep the PI blinded, the Co-I (MBG), who practices in the same building, will be familiarized with each case and will sign the prescriptions. (See Design and Safety sections above.)

The Smartphone Application: Our team has developed a Smartphone application, Fuse: Post-Op Journal, for iOS (Apple) and Android (Google) devices. (Instructional videos are found here: http://www.acljournal.com/.) Once patients download the app, their smartphones alert them 3 times a day to ask them about pain levels (numeric rating scale 0-10), opioid and other medication usage, and side effects of medications. As a default, patients are alerted at 8:00am, 1:30pm, and 7:00pm, however, these

settings can be adjusted to within 3 hours. In the morning, the app also asks patients to record their satisfaction with pain management, pain locations, and hours slept. Patients receive a unique identifier and their responses automatically downloaded into an Excel sheet (Microsoft). Our team has successfully conducted research studies in which patients used the app.[3,11] The following IRB-approved studies have used data from the app. (IRB#: 00092408 and IRB#: 00108695)

Outcome Measures: Participant demographics, medical history, and relevant surgical information will be collected from medical records. Intraoperative and recovery room analgesia regimes will be recorded from patient record and compared between groups, similar to how we have previously reported them.[9]

Pain levels: This is the primary outcome. Patients will record pain levels on Numeric Rating Scale 1-10 on post-operative days 0-6, as described above.

Pain satisfaction, sleep, and side effects: Patients will rate their satisfaction (poor, good, excellent) with their post-op pain management. They will also record any side effects (constipation, nausea, euphoria, other) and hours slept each night. We will record number of tablets used and number of days pain medications are used, track patient-reported breakthrough pain, number of times patients contacted physician staff, and number of "rescue" tablets used.

The following clinical outcomes will be assessed since they can affect the number of pain medications used:

Quality of life will determined with the Emory QOL (equivalent to EQ-5D). EQ-5D is a standardized measure of health status developed by the EuroQOL Group. (11) The patient completes the questionnaire consisting of items that ask patient to rate their level of problems (no problems, slight problems, moderate problems, severe problems, and extreme problems or unable to perform) on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

AIM 2

Design: Aim 2 involves a prospective study of predictors of opioid use. Consecutive patients that are prescribed opioids for post-surgical pain management will be included in this portion of the proposed project. (Patients that enroll in Aim 1 will not be included in this analysis.) All data used for Aim 2 are part of standard of care.

Standard of care for all enrolled patients includes standardized multimodal intra- and post-operative protocols including an adductor canal nerve block at the time of surgery, oral non-opioid (1000 mg acetaminophen) to be used every 8 hours, prescription of 15 tablets of oxycodone (5mg) for breakthrough pain, and education on pain management. Educational pamphlets are administered to all patients, and encouragement to not consume opioids is discussed prior to the patient undergoing surgery. This discussion includes education on proper medication usage, pain management, and disposal of leftover medications with patient and patient's guardian/caretaker (if applicable).

Primary Outcome: Number of pain medication tablets used will be the primary outcome. As part of standard of care, patients will download the smartphone application to track number of pain medications used for 6 days post-surgery.

Predictor Variables: Patient demographics, relevant medical history, and relevant surgical information will be collected from medical records. Importantly, we will also record from medical record any previous or current history of mental disorders (i.e., depression, anxiety), chronic pain, and previous use/prescriptions of pain medications to be used in predictive model. The following outcomes will be physically collected pre-surgery and will also be used in the predictive model:

Quality of life will determined with the Emory QOL (equivalent to EQ-5D), as described above (see Aim 1).

Pain catastrophizing will be determined with the Pain Catastrophizing Scale (PCS), as described above (see Aim 1).

Pain threshold testing will be conducted with digital pressure dolorimeters (Wagner Force One Model FDIX 50™), as described above (see Aim 1).

Risks/discomforts:
We anticipate no additional direct risks or discomfort associated with participation in this study other than that customary of post-ACL reconstruction. The known possible side effects of oxycodone include nausea, vomiting, constipation, lightheadedness, dizziness, or drowsiness. Close monitoring of side effects will be ensued with patient follow-up. A known risk of oxycodone is addiction. Patients will be closely monitored for signs of addiction. For Aim 1, we have a number of additional safety precautions in place to prevent unnecessary risk or discomfort (See "Safety" in Design section above) related to the pain medication randomization (Aim 1). The pain threshold testing has a minimal risk of causing discomfort. However, it is based on the patient's own threshold/level of comfort. Patients will get a chance to feel the sensation on their finger first and see that it is more of a pressure versus painful sensation (the applicator has 1cm diameter and is not pointy).

Potential benefits to subjects/science/society:
We do not anticipate any direct benefit to participants as a result of participating. We do believe the findings from this study will directly benefit future patients by helping understanding the usage and need for pain medications post-ACL reconstruction. This research may help us identify better post-surgical pain management strategies. If the research findings are confirmed, it is possible that less opioids will be needed to treat post-surgical pain, thereby reducing the number of opioids in circulation and mitigating the opioid epidemic in orthopaedics.

7. If applicable: if data/samples collected for this study will be saved/banked/archived for future use, describe plans, who may use the material, and for what purposes (may require a separate repository-specific IRB submission).

   n/a

8. **Community Participation**:

   n/a

9. **Participant selection**:

AIM 1

Participants: Males and females, aged 14-40 years, scheduled for primary ACL reconstruction using quadriceps tendon autograft will be included. Adolescents (14-17 years) will be included because adolescents sustain ACL injuries at a greater rate than adults and undergo standard adult reconstructive procedures.[2] In addition, approximately 17% of ACL reconstructions are performed on individuals in this age group.[1] They are also more likely to be opioid naïve, and are thus at greater risk with their early exposure to opioids. Other inclusion criteria are availability of Smartphone on which patients can download the pain app. Exclusion Criteria involve: revision and/or contralateral ACL reconstruction procedures, allergies to local anesthetics, chronic pain medication use, weight <50 kg, local infections, known coagulopathies, liver dysfunction or renal failure.

AIM 2

Participants enrolled in Aim 1 will not be included in Aim 2.

Participants: Males and females ≥14 years who are undergoing ACL reconstruction performed by Dr. Xerogeanes (PI) will be included. Other inclusion criteria are availability of a Smartphone on which patient can download the pain app. Patients will be excluded if they are: 1) not able to be prescribed the standard of care for opioids (i.e., allergies, contraindications), or 2) self-report of pregnant or breastfeeding.

10. **Informed Consent Process**:

AIM 1

Informed consent will be obtained by study personnel in a private office at the Emory Sports Medicine Complex or Emory Orthopaedics and Spine at Executive Park before any data collection occurs, or remotely (via phone or Zoom). The remote consent process will be assisted by the use of a REDCap E-consent project, which will be able to collect e-signatures of both the subject (and LAR, if necessary) and the member of the research team.
If consent process is being performed via phone or Zoom, the personnel will send the subject or subject's guardian a personalized email link containing a link to the REDCap survey that will let them view and sign the consent if they choose to enroll. The personnel obtaining consent will explain to each potential subject (and his/her legal guardian, if ≤18 years) the protocol and tests to be used in this study and the potential risks and benefits of participation. All study procedures will first be explained in common language and in the same manner during the consent process. Individuals (and legal guardians) will be given ample time to read over the consent form. Adolescents will be given time to privately discuss participation with their guardians, if needed. Following reading and discussion, all participants ≥18 years will review and sign an informed consent form approved by the Institutional Review Board of Emory University prior to initiating any portion of the study. If consent is obtained remotely, subjects (or LAR of subject) will provide e-signature through REDCap, and will receive a copy of the consent that has been signed by the research team member either through encrypted email or a physical copy at their soonest convenience before study participation begins. For individuals aged ≤18 years, both assent from the individual and informed consent

from his/her legal guardian will be obtained prior to participation in any study-related data collections. Assent is also available through REDCap. To prevent coercion and/or undue influence, consent will be obtained from study personnel other than the orthopedic surgeon. Should the individual (and/or legal guardian) wish to not participate, then all study procedures will be ceased and no data collection will occur. Declining to participate in this research study will have no negative repercussions on the medical care the individual receives as a patient of Emory Healthcare.

AIM 2

Using the oral consent document, verbal informed consent will be obtained by study personnel in a private office at the Emory Sports Medicine Complex or Emory Orthopaedics & Spine at Executive Park before any study procedures occur. We will follow similar procedures is listed in Aim 1 above. But since all procedures involved in Aim 2 are standard of care, as well as the large proposed sample size, we have requested verbal consent.

11. **Compensation for time and effort**:

Participants will be compensated a total of $50 (one-time) in the form of Amazon gift cards upon completion of the pain survey that is provided to subjects 2 weeks after their surgery, and can be . A code will be emailed to participants after they complete the pain survey. This code can be applied to Amazon.

12. **Statistical analysis**:

AIM 1

Sample Size: The sample size is based on the primary outcome, pain level. Power analysis was conducted based the non-inferiority nature of our research question. (Hypothesis 1 is confirmed if no statistical difference between groups, meaning non-opioid pain medication is as good as opioid medication). The minimum clinically significant difference for pain levels is 1.2 points on Numeric Rating Scale.[4] Using a conservative estimate of 2 for the standard deviation of pain levels (SD of pain level in our pilot data = 1.9), assuming 80% power, and a one-sided 0.05 type I error, a sample size of 35 participants per group would be required to test the hypothesis. To account for drop-outs, loss to follow-up, or incomplete pain app data, we will inflate same size in each group by 20 participants. Therefore, our sample size for Aim 1 will be 100 participants. As Dr. Xerogeanes performs >200 ACL reconstructions per year (214 ACL reconstructions in 2018), we should have no difficulty in obtaining required sample size.

Analyses: Using independent samples *t*-tests, we will compare pain levels (primary outcome) on post-operative days 1-6, and 2-week post-surgical visit (Hypothesis 1). Independent samples *t*-tests will also be used to compare the number of pain medications used and calculated total morphine equivalents. Chi squares tests will be used to compare the percentage of patients in each group who report side effects (Hypothesis 2).

AIM 2

Sample size: A sample size of 123 participants will be needed, considering a moderate effect size of f^2=0.15, alpha error probability of 0.05, power of 80%, and 11 predictor variables in the model (determined via G*Power 3.1 software). To maximize attrition, this number will be inflated by 5%, therefore, a sample size of 130 individuals will be collected. As Dr. Xerogeanes performs >200 ACL reconstructions per year, we foresee no issue in obtaining this sample size number over two-year grant period. As evidenced by sample size numbers in our previous investigation (n=264 over 2 year period), we have demonstrated success in obtaining these numbers.

Statistical Analyses: Multiple regression analyses will be used to evaluate predictors of post-surgical opioid use. (11 predictor variables: age; sex; diagnosis of mental health disorders, substance abuse, chronic pain; previous opioid usage; previous non-opioid pain medication usage; quality of life; pain catastrophizing; pain threshold scores; and pre-surgical pain levels.) First, Pearson correlation coefficients (r) will be used to examine the association between each of the predictor variables with post-surgical opioid use with a significance level of $p \leq 0.05$. The variables that are significantly correlated with opioids used will then be included in a step-wise regression (variable entry: $p < 0.05$; variable removal: $p > 0.10$) to identify the primary predictors of post-surgical opioid use.

13. **Data and Safety Monitoring and Reporting**: Description of plan for notifying the IRB of reportable events; whether the sponsor requires reporting above and beyond the Emory IRB reporting requirements, and if so, a description of the requirements and plan for meeting them; plan for periodically reviewing data for safety (if more than minimal risk); site monitoring plan for ensuring accuracy and completeness of documentation. See http://irb.emory.edu/documents/DSMB-DSMPGuidance.pdf for guidance.

    A number of procedures will be used to ensure the safety and welfare of study participants.

    Oversight: The principal investigator will provide oversight of the progress and safety of the study. Adverse events are not anticipated, but any event that occurs will be documented and reported according to Emory IRB policies and procedures. A summary of any adverse events will be communicated to the IRB annually as part of the continuing review.

    A clinical research coordinator dedicated to the Sports Medicine division will provide additional oversight and monitoring. This coordinator will monitor the study using the monitoring tools provided at http://www.irb.emory.edu/forms/clinical.html. More specifically, this involves ensuring the team is following regulatory responsibilities and following all reporting requirements. Monitoring will occur on a quarterly basis.

    Confidentiality: The identity of each participant will be protected by using a code number as the only identifier. The master list will be kept in locked file cabinets with access limited to study personnel who have completed CITI training and are listed on IRB.

    Data Accuracy: The principal investigator will be responsible for reviewing protocol compliance, data collection and verification. The data will be reviewed qualitatively during all data collections for each participant.

14. **Confidentiality**:

All records regarding participation in this study will be kept in locked file cabinets in the appropriate laboratories and/or offices of the PI's research team, and stored on password-protected computers/servers in the offices and laboratories of the PI's research team. Data will be securely stored on Emory-approved, password-protected, and encrypted database (BOX). Only those investigators listed on IRB will have access to database. If outside parties help with statistical analysis, identifies will be stripped off first. All PHI will be stripped once study is completed, and no PHI will be used in presentation or publication of study results. The results of the study may be published for scientific purposes, however, individuals' identities will not be revealed and data will not be traceable to any individuals in any resultant publications. The information gathered during this study will be kept confidential to the extent permitted by law.

15. **References/bibliography**:

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