Non-Opioid Prescriptions after Arthroscopic Surgery in Canada (NO PAin): A Randomized Controlled Trial

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SIGNATURE PAGE

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TABLE OF CONTENTS

SIGNATURE PAGE **2**
TABLE OF CONTENTS **3**
LIST OF ABBREVIATIONS **4**
STUDY SUMMARY **5**
1.0 BACKGROUND **6**
2.0 STUDY OBJECTIVES **7**
2.1 Primary Objective 7
2.2 Secondary Objectives 7
3.0 STUDY DESIGN **7**
3.1 Eligibility Criteria 7
3.2 Patient Screening and Enrolment 8
3.3 Randomization Methods 8
3.4 Description of Treatment Arms 8
3.5 Outcomes 9
3.6 Follow-Up 11
3.7 Blinding 11
4.0 STATISTICAL PLAN **11**
4.1 Sample Size 11
4.2 Statistical Analysis 11
5.0 DATA MANAGEMENT **12**
5.1 Case Report Forms and Data Entry 12
5.2 Data Transmissions 12
5.3 Data Discrepancy Inquiries 12
5.4 Security and Back-Up of Data 12
6.0 ETHICS AND DISSEMINATION **13**
6.1 Research Ethics Approval 13
6.2 Consent 13
6.3 Confidentiality 14
6.4 Access to Data 14
6.5 Protocol Amendments 14
6.6 Adverse Event Reporting and Definitions 14
6.7 Safety Monitoring 15
6.8 Ethical Considerations 16
7.0 STUDY TEAM AND MANAGEMENT **16**
7.1 Study Committees 16
8.0 REFERENCES **17**
Appendix 1: Telephone Script and Message for Sending Consent Form 19
Appendix 2: Patient Education Infographic 20
Appendix 3: Members of the NO PAin Multi-Disciplinary Steering Committee 21

LIST OF ABBREVIATIONS

ACI	Autologous Chondrocyte Implantation
ACL	Anterior Cruciate Ligament
AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
EDC	Electronic Data Capture
HCAHPS	Hospital Consumer Assessment of Health Care Provider and Systems
HGH	Hamilton General Hospital
HiREB	Hamilton Integrated Research Ethics Board
LET	Lateral Extra-articular Tenodesis
LPI	Local Principal Investigator
MacSports	McMaster Sports Medicine Research Group
MD	Mean Difference
MPFL	Medial Patellofemoral Ligament
MUMC	McMaster University Medical Centre
NSAIDs	Non-steroidal Anti-inflammatories
ODB	Ontario Disability Benefit
OMEs	Oral Morphine Equivalents
OW	Ontario Works
PHI	Personal Health Information
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SD	Standard Deviation
SLAP	Superior Labrum Anterior and Posterior
SJH	St. Joseph's Healthcare, Hamilton
TTO	Tibial Tubercle Osteotomy
VAS	Visual Analogue Scale
WSIB	Work Safety Insurance Board

STUDY SUMMARY

Title	**N**on-**O**pioid **P**rescriptions after **A**rthroscopic Surgery **in** Canada: A Randomized Controlled Trial
Short Title	NO PAin
Methodology	Randomized controlled trial
Clinical Sites	Multicentre
Primary Objective	To determine, in adult patients aged 18 years and older undergoing outpatient knee or shoulder arthroscopy, whether a non-opioid analgesia approach to postoperative pain, compared to usual care, reduces oral morphine equivalents (OMEs) consumed up to 6 weeks postoperatively.
Secondary Objectives	To determine, in adult patients aged 18 years and older undergoing outpatient knee or shoulder arthroscopy, the effect of a non-opioid analgesia approach to postoperative pain, compared to usual care up to 6 weeks on: 1. Patient-reported pain as measured by a Visual Analogue Scale (VAS) 2. Quantity of OMEs prescribed 3. Number of opioid refills 4. Patient satisfaction as measured by a question modified from the Hospital Consumer Assessment of Health Care Provider and Systems (HCAHPS) questionnaire 5. Adverse event rate
Sample Size	200 patients
Diagnosis and Main Inclusion Criteria	All adult patients (18+ years) undergoing outpatient knee or shoulder arthroscopy (including ligament reconstruction).
Length of Follow-Up	6 weeks postoperatively

1.0 BACKGROUND

Canada has the second highest per-capita opioid use in the world[1,2]. The Government of Canada has declared that "Canada is facing an opioid crisis…the growing number of overdoses and deaths caused by opioids…is a public health emergency"[3]. The problem appears to be worsening: In 2018, there were 4,588 opioid-related deaths across Canada, representing a 52% increase compared to the 3,023 deaths in 2016[4]. In the city of Hamilton, the rate of opioid-related deaths has doubled when compared to the national average[5]. Opioids, though effective for short-term pain relief, are high-risk medications for addiction, tolerance, withdrawal, and fatal overdose[6].

Orthopaedic surgeons prescribe more opioid medications than any other surgical specialty[7,8]. A recent database study across various surgical specialties found that 94% of patients undergoing elective surgery received opioid prescriptions at discharge, and that all orthopaedic surgery patients were well in excess of the recommended opioid prescription guidelines[9]. Furthermore, the vast majority of patients receiving prescription opioids after surgery report having unused narcotics[10]. In other areas of the world, patients take far fewer opioids compared with North-American patients, but report similar satisfaction with pain management[11,12]. One randomized controlled trial (RCT) has shown non-inferiority in patient satisfaction with pain control after fracture fixation treated with acetaminophen alone as compared to acetaminophen and Tramadol[13]. A recent non-randomized prospective study demonstrated that the majority of patients undergoing knee arthroscopy had high rates of satisfaction in managing postoperative pain with only non-steroidal anti-inflammatories (NSAIDs) and acetaminophen prescribed postoperatively[14].

Knee and shoulder arthroscopy are the most commonly performed orthopaedic surgery procedures[15]. Despite this, there are no clinical practice guidelines for postoperative prescriptions. Locally, it is routine practice to prescribe narcotic medications after arthroscopic surgery. We conducted a survey of the Arthroscopy Association of Canada in order to determine the extent of this issue across the country[16]. On average, surgeons reported that 88% of their patients receive a prescription for an opioid medication following knee or shoulder arthroscopy. Canadian surgeons were on average prescribing 156 mg of oral morphine equivalents (OMEs) to patients. This is two to five times as many OMEs as the median amount that patients actually use after knee arthroscopy (35-86 OMEs)[17,18]. Only 66% of surgeons discussed the risks of opioids with their patients. On average, surgeons estimated that only about 12% of their patients requested more opioid medications than initially prescribed. 92% of respondents felt that opioid over-prescription was an issue in surgery as a whole, and 82% believed it was an issue in arthroscopy specifically. There was clear equipoise as to whether non-opioid medications would provide sufficient analgesia post-arthroscopy, with 45% believing they would and 55% believing they would not. Finally, 95% of respondents stated that if high-quality evidence were to support a protocol of limited opioid prescriptions, they would change practice accordingly[16].

Therefore, a study is needed to assess the effectiveness of a non-opioid approach to postoperative pain aimed at reducing overall opioid prescriptions while maintaining adequate postoperative pain control. Recently, a group in London, Ontario conducted a similar study on patients undergoing outpatient general surgical procedures[19]. In that study, the investigators utilized a multi-faceted protocol which included: 1) a standardized non-opioid prescription, 2) a standardized intra-operative protocol, and 3) patient education[19]. The investigators found that their intervention significantly ($p<0.0001$) reduced the number of opioids prescribed by surgeons and the amount of opioids used by patients, while adequately treating postoperative pain.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to determine, in adult patients aged 18 years and older undergoing outpatient knee or shoulder arthroscopy, whether a non-opioid analgesia approach to postoperative pain, compared to usual care, reduces oral morphine equivalents (OMEs) consumed up to 6 weeks postoperatively.

2.2. Secondary Objectives

The secondary research objectives are to determine, in adult patients aged 18 years and older undergoing outpatient knee or shoulder arthroscopy, the effect of a non-opioid analgesia approach to postoperative pain, compared to usual care on patient-reported pain and satisfaction, quantity of OMEs prescribed, number of opioid refills, and any adverse events up to 6 weeks postoperatively.

3.0 STUDY DESIGN

This is an RCT of 200 patients at or over the age of 18 undergoing outpatient knee or shoulder arthroscopy. Patients will be evaluated clinically at 2 and 6 weeks postoperatively. Patients will be recruited from experienced arthroscopic surgeons at 3 hospital sites in Hamilton, Ontario: McMaster University Medical Centre (MUMC), St. Joseph's Healthcare (SJH), and the Hamilton General Hospital (HGH). All research will be conducted according to international standards of Good Clinical Practice and institutional research policies and procedures.

3.1 Eligibility Criteria

3.1.1 Inclusion Criteria

1. Patients undergoing outpatient knee or shoulder arthroscopy for any of the following procedures:

Knee	Shoulder	Shoulder and Knee
ACL reconstruction (with or without LET) MPFL reconstruction (**not** including TTO) Chondroplasty Meniscectomy Meniscal repair Meniscal transplant Microfracture ACI Fixation of unstable osteochondral lesion	Subacromial decompression Rotator cuff repair Shoulder stabilization Superior capsule reconstruction Biceps tenotomy/tenodesis Capsular release SLAP repair	Diagnostic arthroscopy Irrigation and/or debridement Loose body removal Synovectomy

2. Patients ages 18 and older
3. Patients who have the ability to speak, understand, and read English
4. Provision of informed consent

3.1.2 Exclusion Criteria

1. Patients who take or are on a home dose of an opioid medication (i.e. once daily or more)
2. Patients involved in ongoing litigation or compensation claims for any injury (e.g. Work Safety Insurance Board, WSIB)
3. Patients involved in another research study that requires a specific post-operative pain control medication regimen

4. Patients undergoing a knee or shoulder arthroscopy procedure that will likely have an operative time greater than 3 hours
5. Patients who will undergo concomitant open surgery
6. Patients who require overnight admission
7. Patients with a contraindication or allergy to NSAIDs, acetaminophen, or morphine and hydromorphone
8. Patients diagnosed with renal disease or cardiac disease
9. Patients who are scheduled for/plan to have an additional surgical procedure during the 6-week follow-up period
10. Patients who will likely have problems, in the judgement of the investigator, with maintaining follow-up
11. Any other reason(s) the investigator feels is relevant for excluding the patient

*In the event that the patient does not meet the specific eligibility criteria postoperatively (e.g. patient required overnight admission unexpectedly), the patient will be withdrawn from the study (if discovered prior to the 6-week follow-up) and/or excluded from the final analysis (if discovered after the final 6-week follow-up).

3.2 Patient Screening and Enrolment

Patients ages of 18 and older who present to a recruiting hospital for a knee or shoulder injury will be screened prior to their arthroscopic procedure. To screen patients for eligibility, designated study personnel at each clinical site will be in close contact with the participating site investigators (surgeons) and their administrative staff to help identify which patients are scheduled for a knee or shoulder arthroscopic procedure each month. The surgeon, clinic staff, or administrator staff will ask the potentially eligible patient if they are comfortable being approached about a clinical research study either during a preoperative clinic visit, via a phone call, or email. If the patient agrees, study personnel will contact the patient either in person OR via phone call at some point prior to surgery (**Appendix 1**). For all remote consent calls, the study personnel will email the patient the consent form (in Word or PDF format) at the beginning of, or prior to the call. The patient will be informed that they are able to abstain from deciding until the date of the procedure. The study personnel will screen the patient for eligibility by going through all items listed on the Screening Form and if eligible, proceed with going through the informed consent form and obtaining informed consent from the patient. If the patient agrees to participant, they will be asked to sign/initial the consent form where indicated. For a remote consent call, patients will be instructed to send a signed scanned copy to the study personnel via email or will be provided a paper consent form to complete prior to their surgery. Refer to **Section 6.2** for more information regarding the consent process. All screened patients will be classified as included, excluded, or missed (eligible, but not randomized due to error).

3.3 Randomization Methods

Eligible patients will be randomized using the centralized 24-hour computerized randomization system on REDCap™ Cloud, that allows for automated internet based randomization to allocate patients to the control (standard of care) or intervention (non-opioid prescription and infographic) group. Patients should be randomized as close as possible to the time of surgery as permitted by site-specific operating room scheduling.

3.4 Description of the Treatment Arms

<u>3.4.1 Intervention Group: Non-Opioid Prescription and Infographic</u>

The study intervention will involve 3 components:

1) **A standardized non-opioid prescription:** A prescription for Naproxen 500mg PO BID PRN x 60 tabs, Acetaminophen 1000mg PO Q6H PRN x 100 500mg tabs and Pantoprazole 20mg PO daily x 30 tabs (to be taken only while utilizing Naproxen). The inclusion of two over-the-counter analgesic medications provided on the prescription accomplishes two goals: a) it legitimizes these medications and suggests that the healthcare providers truly believe in and recommend their use, and b) it allows for patients on Ontario Disability Benefit (ODB) or Ontario Works (OW) access to medications that may otherwise be cost-prohibitive. In the case of a Naproxen intolerance, a prescription for Meloxicam 15mg PO BID PRN x 60 tabs will be given.
2) **A limited opioid "rescue prescription"**: A prescription of Hydromorphone 1mg PO Q4H PRN x 10 tabs will be included on a separate prescription. In cases of Hydromorphone intolerance, a prescription for Morphine 5mg PO Q4H PRN x 10 tabs will be provided. Patients will be instructed to use the opioid prescription only in cases where they are unable to achieve adequate pain control using the non-opioid prescription. In the case of a severe hydromorphone allergy, patients will receive Oxycodone 5mg PO QH4 PRN x 10 tabs. Included with the opioid prescription will be a prescription for Senna 1-2 tabs QHS PRN for constipation.
3) **Patient education infographic:** The infographic will contain information on how to take the prescribed medications, along with instructions that the morphine rescue prescription should only be used in cases where the non-opioid pain medications are not providing satisfactory pain control. The infographic will also contain information about the risks of opioids and prevalence of opioid misuse and abuse. Finally, it will include information on appropriate storage and disposal of opioids (**Appendix 2**).

Patients in the intervention group were prescribed all medications on an as needed basis based on pain levels but were encouraged to utilize both naproxen and acetaminophen even when experiencing mild pain in the first week following surgery. The naproxen dosing was higher than the recommended starting dose in Canada. After consultation with a perioperative pharmacist as well as a review of the existing literature, 500mg BID was chosen to provide optimal analgesia in the postoperative setting.

3.4.2 Control Group: Standard of Care

The control group is standard of care, which typically includes a prescription for an opioid. The standard of care prescription varied by surgeon and procedure and included oxycodone, codeine or hydromorphone, ranged from 20 tablets to 80 tablets and were prescribed to be taken on an as needed basis. Patients in the standard of care group did not receive standardized counselling surrounding the use of NSAIDs or acetaminophen for minor or moderate postoperative pain and these medications were not routinely prescribed postoperative in this group. Patients were allowed to use these over-the-counter medications at their own discretion.

3.4.3 Standardization of Allocating the Control and Intervention

Prior to starting the study, each surgeon investigator will provide the study team with their standard of care prescriptions for each procedure they perform as part of their practice (as per the procedures listed in **Section 3.1.1**, inclusion criterion 1). The non-opioid intervention prescription and infographic will also be prepared prior to starting the study. This way, the allocated prescription can be placed on the patient's chart prior to surgery by the study team to avoid the potential for surgeon error. The surgeon/resident will simply need to review and sign the prescription before it is given to the patient.

In addition to reducing the potential for prescription error, these methods eliminate the risk of surgeons modifying their practice to prescribe less opioids part way through the study if they feel the intervention group is effective as surgeons will be unable to be blinded to the patient's allocation group (Note: A Medical Monitor will be independently and objectively monitoring for safety based on a regular blinded review of the data. See **Section 6.7**). The decision to add additional deep vein thrombosis prophylaxis to the patient prescription is left to the discretion of the treating surgeon on a case by case basis in both the control and intervention groups.

3.4.4 Standardization of Peri-Operative Pain Management

All patients will receive a standardized peri-operative pain management protocol, which will include: a) acetaminophen 1000mg PO q6h PRN, b) ketorolac (15-30mg IV x 1), c) ondansetron (4-8mg PO/IV q8h PRN), d) gravol (25-50mg PO/IV q6h PRN), e) an extra-articular injection of 10mL of 0.5% bupivacaine with epinephrine into the soft tissues surrounding the portal sites, f) Oxycodone 5mg regular release PO x 1 in recovery, and g) hydromorphone 1mg PO q4h PRN (or Morphine or Oxycodone if intolerant/allergic, see 3.4.1 for details). Note that dose ranges are provided to allow for adjustments based on patient weight if necessary.

3.5 Outcomes

3.5.1 Primary Outcome

The primary outcome is the number of total OMEs consumed at 6 weeks postoperatively, as determined by a patient-reported medication diary.

3.5.2 Secondary Outcomes

Secondary outcomes include: 1) patient-reported pain (VAS), 2) patient-reported satisfaction with pain control (HCAHPS), 3) number of OMEs prescribed, 4) number of opioid refills, and 5) any adverse events up to 6 weeks postoperatively.

3.5.3 Outcome Measures

Patients will be provided with a medication and pain diary to complete (as a Word document to update on the computer or on paper) daily from the time of surgery to the 2-week follow-up visit. The research personnel will check the medication and pain diary at the 2-week visit and update the case report forms (CRFs) with any and all information. The medication and pain diary will be used to measure the number of OMEs consumed (primary outcome), the number of OMEs prescribed and refills (secondary outcomes), and daily pain VAS scores (secondary outcome). At the 6-week follow-up patients will also be asked the total amount of opioid medication they have taken.

Patients will complete self or interview-administered outcome questionnaires during the routine follow-up visits at 2 weeks and 6 weeks. The **VAS** will include a 100mm line, on which patients will be asked to rate their average pain since their surgery. Higher scores indicate higher levels of pain. The VAS is one of the most frequently used pain rating scales in clinical practice and research[21]. The VAS is a validated unidimensional scale that is easy to use, requires no verbal or reading skills, and is sufficiently versatile to be employed in a variety of settings[22-24]. The **HCAHPS** is a validated and nationally standardized survey designed to evaluate patient perspectives of hospital care[25]. As per previous research evaluating patient satisfaction following orthopaedic procedures, we used the following modified question from the HCAHPS questionnaire related to satisfaction with pain relief, answered on a Likert scale (never, sometimes, usually, or always): "In the time after surgery, how often was your pain well controlled?"[14,26]. For a dichotomous analysis, responses of "always" and "usually" will be grouped as satisfied patients, and responses of "sometimes" or "never" will be grouped as

unsatisfied patients. Patient satisfaction will be measured at the 2- and 6-weeks follow-up appointments. Adverse events, defined as any symptom, sign, illness, or experience that develops or worsens in severity during the course of this study, will also be documented (**Table 1**).

Table 1: Schedule of events

Data Collection	Enrollment	2 Weeks	6 Weeks
Screening and Informed Consent	●		
Enrolment Data (Demographics)	●		
Follow-Up Form		●	●
Medication Diary OMEs consumed OMEs prescribed Opioid refills		#	
Total OMEs consumed			●
Visual Analogue Scale (VAS)		#	●
Patient Satisfaction (Question from HCAHPS)		●	●
Adverse Events		x	x

x – if applicable, # - daily up to the 2-week visit

3.6 Follow-Up

Study participants will be followed at 2 weeks (window between 1 and 3 weeks) and 6 weeks (window between 5 and 7 weeks) postoperatively. Visits that occur outside of these windows must be marked as early or late, respectively. This follow-up schedule is in accordance with the current practice at each clinical site and does not require extra visits or costs to the patients. Patients who are unable to attend the follow-up appointments will be contacted by telephone to complete the applicable questionnaires and CRFs for all visits up to and including 6 weeks.

3.7 Blinding

Given that patients in the intervention group will receive a pamphlet explaining how to use their prescription allocation, patient blinding is not feasible. Surgeons cannot be blinded as they will need to sign the prescriptions and provide any necessary advice about the medications being prescribed. Outcome assessors and data analysts will be blinded.

4.0 STATISICAL PLAN

4.1 Sample Size

Based on prior literature, patients undergoing knee and shoulder arthroscopy can be expected to consume a median of about 100 OMEs post-surgery without intervention[18]. Given that we are prescribing 75 OMEs in the intervention group, and patients have been shown to consume 25-50% of their prescription depending on whether they are undergoing knee or shoulder arthroscopy, respectively, we expect that the overall prescription consumption will be 33% of the prescribed amount (i.e. 25 OMEs). Using an alpha-value of 0.05, power of 80%, a standard deviation of 155 OMEs[18], the required sample size is 68 patients per group, for a total sample size of 136. According to Thoma *et al*., estimated sample sizes should be increased by 10-40% to allow for loss to follow-up and unforeseen circumstances[27]. Thus, based on the most conservative estimate of this guidance, we will increase our sample size by 40% for a total of 190 patients, rounded to 200 (100 per group). Allowing for patients who need to be excluded, those who choose not to participate, and loss to follow-up, we estimate we will need to screen approximately 300 patients for eligibility for a 66% inclusion rate. Based on previous caseloads (1300 knee and shoulder arthroscopy cases per year in total in Hamilton), and

allowing for holidays and other variations (e.g. summer shutdown), we very conservatively estimate that this will require 6 months of screening and enrolment.

4.2 Statistical Analysis

We will adopt the intention to treat principle for all analyses—that is, patients will be retained in their randomized groups for all analyses. The baseline characteristics of the patients will be summarized by group, reported as a mean (standard deviation [SD]) or median (first quartile, third quartile) for continuous variables and count (percent) for categorical variables. We will use multiple imputation to handle missing data to enable an intention to treat analysis[29]. No interim analyses are planned. All tests will be 2-sided with $\alpha = 0.01$. We will use SAS 9.4 (Cary, NC) to perform all analyses.

4.2.1 Primary Analysis

The number of OMEs consumed will be compared between groups using an independent samples t-test and presented with a p-value as well as a mean difference (MD) with 95% confidence intervals (CIs).

4.2.2 Secondary Analyses

We will perform an independent samples t-tests to test for differences in 2-week VAS scores and OMEs prescribed between groups. We will also plot mean daily VAS scores as per the medication and pain diary over time up to 2 weeks as a descriptive analysis. The proportion of adverse events, satisfied patients, and opioid refills will be compared between groups using an odds ratio. Each secondary outcome will be quantified using descriptive statistics and 95% CIs.

4.2.3 Subgroup/Sensitivity Analyses

We plan to conduct 3 subgroup analyses comparing 1) shoulder versus knee arthroscopy patients; 2) patients who received a regional block of any kind as a part of their anesthetic versus those who did not; and 3) males versus females. We plan to perform a logistic regression and include treatment by subgroup interactions to assess whether the magnitude of the treatment effect is significantly different between these subgroups.

5.0 DATA MANAGEMENT

5.1 Case Report Forms and Data Entry

The CRFs will be the primary data collection tool for the study. All data requested on the CRF must be recorded. An Electronic Data Capture (EDC) system (REDCap™ Cloud) will be used to submit data to the Methods Centre located at McMaster University. Site personnel will receive a unique login and password for the REDCap Cloud system and will be able to view and modify data for participants recruited at their clinical site. Upon receipt of the data, the personnel at the Methods Centre will make a visual check of the data and they will query all missing data, implausible data, and inconsistencies.

5.2 Data Transmissions

Data will be transmitted from the clinical sites to the Methods Centre using the REDCap Cloud system. The data entry screens in the REDCap Cloud system will be similar to the paper CRFs. Data integrity will be enhanced by using the REDCap Cloud system through a variety of mechanisms for checking data at the time of entry including referential data rules, valid values, range checks, and consistency checks against data already stored in the database. Site personnel will be able to view and modify data for participants recruited from their clinical site only. Each time data is submitted or modified, it will be validated by Methods Centre personnel.

5.3 Data Discrepancy Inquiries

Once data are submitted, additional errors will be detected by the program within the EDC system to detect missing data or errors. Site personnel will be notified of these errors through regular communication with the Methods Centre. To respond to queries, study personnel should check the original forms for inconsistency and check other sources of participant records to determine the correction. Site personnel will then modify the data in the EDC system to reflect the correction and resubmit data to the Methods Centre in order to resolve the query.

5.4 Security and Back-Up of Data

All CRFs must be kept secure in locked cabinets or other enclosures that are accessible only to study personnel. All electronic data must be password-protected and accessible only to study personnel. The Methods Centre will be responsible for backing up all data submitted through the REDCap Cloud system. The REDCap Cloud system is hosted on local, McMaster-based servers. Individual clinical sites and personnel will be provided with a unique user ID and granted access to only their local site information. Data exports will be strictly limited to the Methods Centre only.

6.0 ETHICS AND DISSEMINATION

6.1 Research Ethics Approval

This protocol, CRFs, informed consent form, and any patient recruitment material will need to be reviewed and approved by the Hamilton Integrated Research Ethics Board (HiREB) for all clinical sites participating in the trial.

6.2 Consent

Any patients who are deemed to meet all eligibility criteria should be approached to discuss participation in the trial by someone on the study team who is knowledgeable about the study. In order to obtain informed consent, study personnel should follow the below procedures:

- Present study information in a manner that is understandable to the patient.
- Discuss the study with the patient and answer any questions they ask.
- Allow the patient an opportunity to discuss participation with their family, friends, or family physician if desired.
- Confirm that the patient understands the risks and benefits of participating in the study and that their participation is voluntary.
- Complete and obtain signature(s) from the patient on the informed consent form.
- Provide/send the participant with a paper/electronic copy of the signed consent form.

Consent may be obtained electronically or using pen and paper consent forms, as approved by HiREB. If potential participants are contacted by telephone, documenting written informed consent will involve the following procedures:

- The study team confirms the potential participant's interest in learning more about the study and verifies the mailing address, email address, cell phone (for texting), or fax number to which the consent form can be sent.
- A blank consent form is mailed, emailed, texted, or faxed along with a message that introduces the study and explains when the phone conversation will occur (**Appendix 1**).
- After the potential participant has received the document, a member of the study team calls the potential participant and walks through the entire document over the phone, answering questions and making notes about the potential participant's questions. Time and date of the conversation should be recorded.

- Once all questions are answered, the participant signs the consent form if they are willing to participate. S/he returns the consent form by mail, email, text, or fax.
- Once received, the study team member who conducted the consent conversation should sign the consent form and date with today's date. To explain the discrepancy, this individual should also write a note on the consent form stating that the participant's consent was obtained by phone on xx date (the date the participant signed.)
- The participant should receive back a fully-signed copy of the consent form for their records.

The process of obtaining and documenting informed consent will be completed in accordance with local Good Clinical Practice recommendations and HiREB requirements. Upon providing informed consent, trial participants will be followed for 6 weeks from their arthroscopic procedure. Given the short follow-up time, the need for a regular reassessment of consent will not apply; however, participants may withdraw their consent at any time.

6.3 Confidentiality

Information about study participants will be kept confidential and will be managed in accordance with the following rules:

- All study-related information will be stored securely at the clinical site.
- All study participant information will be stored in locked file cabinets and be accessible only to study personnel.
- All CRFs will be identified only by a coded participant number.
- All records that contain participant names, or other identifying information (e.g. consent forms and contact information forms), will be stored separately from the study records that are identified only by the coded participant number and initials.
- All databases will be password protected.

In the event that a participant revokes authorization to collect or use personal health information (PHI), the clinical site retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. primary outcome data) at the end of their scheduled study period.

6.4 Access to Data

Only the Methods Centre will have access to the full study dataset. Data for the primary publication will be analyzed exclusively by the Methods Centre. Requests for access to the full study dataset for secondary publications are encouraged and can be initiated through a written request to the Methods Centre personnel. All requests will be reviewed by the Principal Investigators.

6.5 Protocol Amendments

Any amendments to the study protocol which may affect the conduct of the study, or the potential safety of or benefits to participants (e.g. changes to the study objectives, study design, sample size, or study procedures) will require a formal amendment to the protocol. Any protocol amendments will be approved by the Principal Investigators. The Methods Centre will submit amendment requests to HiREB in order to obtain approval for the amendment. Administrative changes (e.g. minor corrections or clarifications that have no effect on the way the study is conducted) will not need to undergo a formal amendment process and will be communicated to each clinical site when applicable.

6.6 Adverse Event Reporting and Definitions

6.6.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the course of this study.

6.6.2 Serious Adverse Event

AEs are classified as serious or non-serious. A serious adverse event (SAE) is any AE that is any of the following:

- Fatal
- Life threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event

6.6.3 Unanticipated Problems Resulting in Risk to Participant or Others

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

- Unexpected in nature, severity, or frequency (e.g. not described in study-related documents such as the ethics-approved protocol or consent form, etc.).
- Related or possibly related to participation in the research (i.e. possibly related means there is reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic, or social harm).

6.6.4 Serious Unexpected Adverse Drug Reactions

A serious adverse drug reaction means a noxious and unintended response to a drug that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death. An adverse drug reaction is considered unexpected when its nature (i.e., specificity or outcome), severity or frequency is either not identified, or is not consistent with the term or description used in the product labelling.

6.6.5 Adverse Event Reporting

Clinical sites are responsible for reporting SAEs and serious unexpected adverse drug reactions immediately to the Methods Center via the REDCap Cloud system. Significant new information on ongoing SAEs should also be provided promptly to the Methods Center via the REDCap Cloud system. Unanticipated problems resulting in risk to participants or others are also to be reported promptly to the Methods Center.

The Methods Center will inform HiREB any serious unexpected adverse drug reaction within 48 hours of becoming aware of the information.

6.7 Safety Monitoring

A Medical Monitor will be sent regular updates to monitor the study data for safety. The Medical Monitor will provide medical expertise for study oversight and safety concerns and is required to provide recommendations about starting, continuing, and stopping the study. The Medical Monitor is an independent physician.

Specific responsibilities of the Medical Monitor include:

- reviewing study reports;
- protecting the safety of the study participants;
- reporting on the safety of the study;
- considering factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- making recommendations to the Principal Investigators concerning continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the treatments under study; and
- ensuring the confidentiality of the study data.

Methods Centre research personnel will prepare quarterly reports for the Medical Monitor to review. Reports will include enrollment over time and listings of demographics and baseline characteristics, excluded subjects, early withdrawals, CRF completeness, adverse events and serious adverse events. The Medical Monitor may direct additions and other modifications to the reports on a one-time or continuing basis. The Medical Monitor may request a formal meeting with the Principal Investigators and Research Manager at any time to discuss the conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered, as well as any patient safety concerns.

Following each quarterly review, the Medical Monitor will provide a recommendation to continue or terminate the study. A recommendation to terminate the study should be transmitted to the Research Manager and Principal Investigators immediately, who would then notify the site investigators and HiREB immediately. All patients currently enrolled in the study would also be notified.

6.8 Ethical Considerations

This study is to be conducted according to the US and international standards of Good Clinical Practice and International Conference on Harmonization guidelines, applicable government regulations, and institutional research policies and procedures.

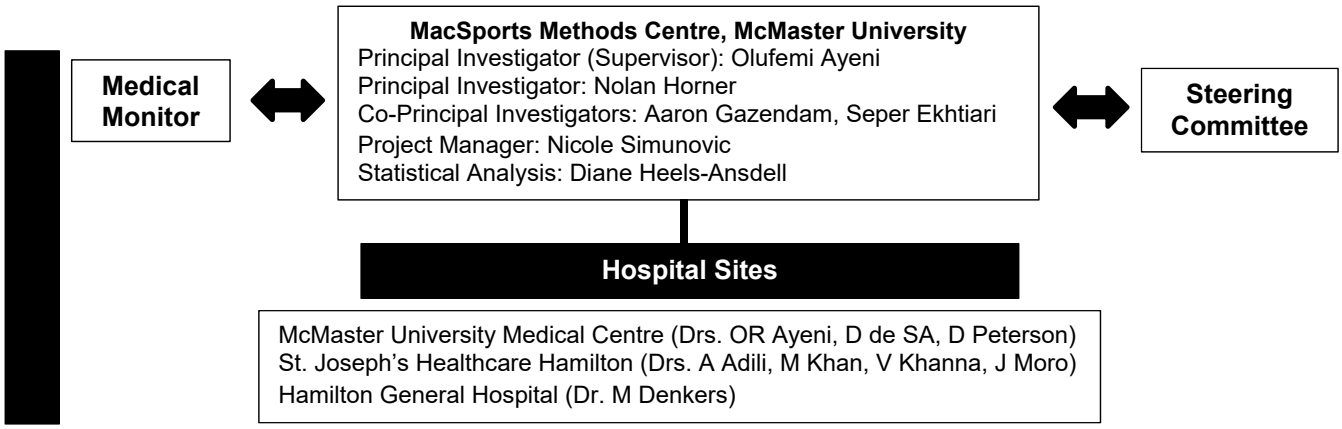
7.0 STUDY TEAM AND MANAGEMENT

The study will be managed through the MacSports Methods Centre at McMaster University. Dr. Ayeni is the Director of this research group as part of the Centre for Evidence-Based Orthopaedics at McMaster University. Dr. Ayeni will be responsible for the daily high-level oversight and conduct of this study. Dr. Ayeni will be supported by a multi-disciplinary team of co-investigators and a core team of Co-Principal Investigators (**Figure 1**).

7.1 Study Committees

The Steering Committee will provide guidance and direction to the overall study. This committee consists of world experts in their respective fields and many members have experience leading large multi-centre clinical trials (**Appendix 3**). Specific responsibilities of the Steering Committee include reviewing and approving the study protocol and working together to resolve any challenges that arise during the study.

Figure 1: Study organization


Medical Monitor
MacSports Methods Centre, McMaster University
Principal Investigator (Supervisor): Olufemi Ayeni
Principal Investigator: Nolan Horner
Co-Principal Investigators: Aaron Gazendam, Seper Ekhtiari
Project Manager: Nicole Simunovic
Statistical Analysis: Diane Heels-Ansdell
Steering Committee
Hospital Sites
McMaster University Medical Centre (Drs. OR Ayeni, D de SA, D Peterson)
St. Joseph's Healthcare Hamilton (Drs. A Adili, M Khan, V Khanna, J Moro)
Hamilton General Hospital (Dr. M Denkers)

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8.0 REFERENCES

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Appendix 1: (A) Telephone Script and (B) Message for Sending Consent Form

(A) No PAIN Telephone Consent Script

Following introduction to the study by the surgeon, permission to be contacted via telephone is obtained and communicated to the research team. The patient is either given the consent form in person or it is sent via email for a chance to review before they are contacted.

Below is a script to follow when contacting patients.

Introduction

1) Study Personnel: "Hello, my name is _____ and I am calling regarding a study that aims to reduce the over prescription and use of narcotic pain medications that you had discussed in clinic with your surgeon. Do you have some time to talk?"

    a. Yes -> Proceed to explain background information (2)
    b. No -> Ask if they would be available at another time and schedule a time to call back. If not interested, inquire as to why not and complete a screening form for an excluded patient.

2) "Great. Have you had a chance to look over the information sheet provided to you in clinic or over email? Let's go through it all together now. Feel free to ask any questions as we go."

Informed Consent Form

3) Go through the ICF in its entirety.

Consent

4) "Would you be interested in participating?"
    a. Yes -> "Great. Please ensure you sign the consent form I sent you via email and be sure to initial each page. Please send a scanned copy back to me via email or text. Now, I'd like to complete some questions about how you're feeling today if you'd like to continue, or we can do it in person prior to surgery."
        i. In person -> End the call after confirming they received the consent form to sign and thank them for agreeing to participate. Let them know they can contact you if they have any questions at any point and provide your contact information.
        ii. Continue questions -> complete baseline questionnaires.
    b. No -> "May I ask why?" Try to answer any questions or concerns and gauge interest. If they do not want to provide consent, thank them for their time then fill a screening form for an excluded patient.

(B) Email Draft to Prospective Participants

Hello [Participant name],

I am reaching out to you regarding the study that is looking at reducing the over prescription of narcotic pain medications, also known as opioids, after surgery. You had initially discussed this with your surgeon at the clinic. As discussed, the study information sheet is attached to this email. Please review this information sheet prior to the call with the research personnel and make note of any questions you have for us.

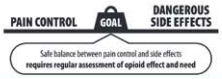
We will give you a call on or around [date and time] to explain the study in more detail.

Regards, [Your name]

Appendix 2: Patient Education Infographic

Recommendations:

- The use of ice, heat or physical therapy can reduce inflammation and pain.
- Your pain should subside daily after your surgery. Many patients do not use any opioids after the third day after surgery.
- Complete your medication diary, and keep track of your medication use, including opioids and non-opioid medications.
- Ask your doctor about whether you need additional pain management strategies, including prescription renewals or alternative treatments.
- With opioids, there is a fine balance between effective pain control and dangerous side effects. If you have questions, please contact the Research Team.
- When you no longer need your medication to help control your pain; remember to return anything you have not used to your pharmacy. They can dispose of it safely for you.



If you have any questions, please contact your Doctor, or the Research Team

Study Contact Information

Research Team

no.pain.hamilton@gmail.com

Research Coordinator

Andrew Duong
duonga@mcmaster.ca
905-923-2126

Non-Opioid Prescriptions after Arthroscopic Surgery in Canada: A Randomized Controlled Trial

Reducing Pain Without Opioids

Pain Medication

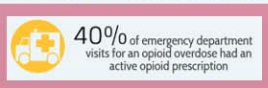
You have received a prescription for Acetaminophen (Tylenol) and Naproxen (Aleve, Naprosyn). We recommend these as **"FIRST STEP"** pain medications.

- Acetaminophen can be taken every 4 hours
- Naproxen can be taken every 12 hours for pain.
- For the first week, take both of these medications on a regular basis even when experiencing minimal pain in an effort to stop post-operative pain before it starts.
- Only in cases where pain persists 1-2 hours after use of Acetaminophen and Naproxen should the opioid prescription (Morphine) be used.

Opioids are intended to improve your pain enough so that you are able to do your day to day activities, but **not reduce your pain to zero.**

The Risk of Addiction

Many people have used opioids without problems. However, serious problems, including overdose and addiction, have happened. It is important to follow the instruction on the prescription and use the lowest possible dose for the shortest possible time, and to be aware of signs of side effects or dependence.

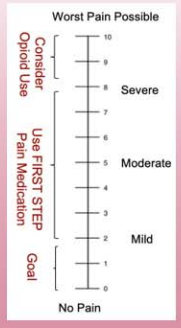


Courtesy of Gomes et al (2018). The BMJ, *362*, k3207.

Managing Opioid Use

Pain management after surgery is about reducing pain so that you can return to normal activities. The goal is to not hit zero on the pain scale, but to avoid levels 8 and above.

Only consider opioid use when your pain levels are more than Severe (level 8).



Potential Side Effects of Opioid Use

Nausea, Constipation, Dizziness, Drowsiness, Reduced Physical or Mental Abilities, Depression, Respiratory Issues, Reduced Blood Pressure, Heart Palpitations, Irregular Heartbeat, Problems Sleeping, Including Sleep Apnea, Vision Problems. Other underlying health issues may put you at higher risk or worsen the potential side effects.

Appendix 3: Members of the NO PAin Multi-Disciplinary Steering Committee

Member	Role
Dr. Olufemi Ayeni	Dr. Ayeni will be acting as the Principal Investigator, Scientific Mentor, and Supervisor for this study. He is an attending orthopedic surgeon and site chief at MUMC. Dr. Ayeni is a world expert in arthroscopic surgery and has been invaluable in guiding in such a way that it is acceptable to other arthroscopic surgeons in the city. Dr. Ayeni's training and experience with conducting research and successfully leading large RCTs will be invaluable to the success of this study. He has successfully conducted the Femoroacetabular Impingement Randomised Controlled Trial (FIRST), which was completed in 2019. He leads several other large trials.
Dr. Nolan Horner	A 4th year orthopaedic surgery resident at McMaster University, with an extensive track record of high impact publications and project completions and the Principal Investigator for the project. Dr. Horner had led in the development of all stages of this research question and trial design.
Dr. Caitlin VanDeCapelle	A staff anesthesiologist at HHS with a clinical interest in peri-operative pain control and will advise on the pain management in the intraoperative and immediate peri-operative period.
Dr. Seper Ekhtiari	A 3rd year orthopaedic surgery resident at McMaster University who is currently taking time off clinical duties to complete his Master's degree at McMaster University. Dr. Ekhtiari will act as a Co-Principal Investigator for this trial.
Dr. Aaron Gazendam	A 2nd year orthopaedic surgery resident at McMaster University and will be acting as the Co-Principal Investigator and Project Officer for the project. Starting August 2020, Dr. Gazendam will be taking one year off clinical duties to complete his Master's degree at McMaster university. He will aid in day-to-day running of the trial and organization of the research assistants.
Franca Mossuto	A peri-operative orthopaedic service resource nurse at HHS, is actively involved in orthopaedic clinical trials at HHS. She will coordinate education sessions with the peri-operative nursing teams and will ensure that the proposed methodology will be feasible in the clinical setting at HHS.
Eric Romeril	Has a clinical interest in peri-operative pain control and works with the total joint arthroplasty service as HHS to reduce opioid consumption following joint replacement surgery. He will advise on the optimal non-opioid pharmacologic pain management strategies peri-operatively.
Steve Phillips	A patient who previously underwent an anterior cruciate ligament reconstruction in Guelph and had some of their follow-up care performed at HHS. Steve Phillips will act as the patient experience advisor.