Non-**O**pioid **P**rescriptions after **A**rthroscopic Surgery **in** Canada (**NO PAin**): A Randomized Controlled Trial

Statistical Analysis Plan

Version 1.0

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Document History

Date (dd-mmm-yy)	Drafted/Revised By:	Version Number	Description of Amendments
27-Apr-2022	S. Ekhtiari, A. Gazendam, N. Horner, N. Simunovic, D. Heels-Ansdell, O.R. Ayeni	1.0	First draft of SAP based on original trial protocol

INTRODUCTION

NO Pain is a multi-centre, randomized controlled trial (RCT) evaluating adult (18+ years of age) patients undergoing outpatient knee or shoulder arthroscopy. Patients were randomized to an opioid sparing postoperative protocol (intervention) or the current standard of care (control). The intervention consisted of a standardized non-opioid analgesic prescription, a limited rescue opioid prescription, and a patient education infographic. The control was defined as the treating surgeons' pre-trial postoperative analgesic regimen, which typically included an opioid prescription. Patients were followed up at 2 and 6 weeks postoperatively. The primary outcome was the total amount of opioids consumed at 6 weeks postoperatively. Secondary outcomes included patient-reported pain and satisfaction, quantity of oral morphine equivalents (OMEs) prescribed, number of opioid refill requests completed (i.e., number of patients who requested and received a refill script), and any adverse events up to 6 weeks postoperatively.

Primary Endpoint

The primary outcome is the total amount of opioids consumed in the 6-week postoperative period. This was calculated as OMEs based on published conversion methods[1] **(Appendix 1).**

Secondary Endpoints

The secondary outcomes are the following measured at 6 weeks:

1) Patient-reported pain, as measured on a 100-point Visual Analogue Scale (VAS)
2) Patient-reported satisfaction, measured using a modified question from the Hospital Consumer Assessment of Healthcare providers and Systems (HCAHPS) questionnaire
3) Number of OMEs prescribed at time of hospital discharge
4) Proportion of patients who had an opioid refill request completed within 6 week postoperatively
5) Adverse events up to 6 weeks postoperatively

Scope of the Analysis plan

This Statistical Analysis Plan presents the analyses for the NO PAin primary manuscript. The manuscript will include 6-week follow-up data for the trial.

ANALYSIS PLAN

Blinded Analysis

The primary analysis will be completed using blinded data. Treatment groups will be identified using coded identifiers (i.e., treatment A and B). Analyses will be performed and interpretations documented based on these blinded treatment groups, prior to unblinding.

Presentation of Data

The baseline demographic characteristics and surgical procedures performed will be summarized descriptively by treatment group and reported as mean (standard deviation [SD]), median (interquartile range [IQR]), or count (percent) as appropriate **(Tables 1 and 2)**. All statistical tests will be 2-tailed with $p < 0.05$ considered statistically significant. All analyses will be performed on an intention-to-treat basis.

Primary Outcome Analysis

The primary analysis will be an independent samples t-test to compare the total 6-week OMEs consumed by each group **(Table 3).** Patients who were randomized but did not undergo surgery will be

excluded from the analysis. For all patients who did undergo surgery, missing data will be handled using the method of multiple imputation. The effect size will be reported as the mean difference in OMEs consumed, with associated 95% confidence interval (CI) and p-value. If the data are not normally distributed, a log transformation will be performed prior to conducting the t-test. If following log transformation, the data are still not normally distributed, we will conduct a Wilcoxon rank sum test on the untransformed data, instead of a t-test.

Secondary Outcomes Analysis

The secondary outcome analyses will be performed for patient-reported pain, patient-reported satisfaction, number of OMEs prescribed, incidence of opioid refill requests, and adverse events up to 6 weeks **(Table 3).**

Continuous outcomes will be analyzed using an independent samples t-test and reported as mean differences with corresponding 95% CIs and p-values. Similar to the analysis of the primary outcome, if the data are not normally distributed, we will first log transform and if the data are still not normally distributed, we will use the nonparametric Wilcoxon rank sum test. Dichotomous outcomes will be analyzed using a chi-squared test and reported as odds ratios with 95% CIs and p-values. As specified in our original protocol, patient-reported satisfaction will be dichotomized from a four-point Likert scale to include the response 'always' and 'usually' as satisfied patients, and 'sometimes' and 'never' as unsatisfied patients. Missing data will be handled using the method of multiple imputation. No adjustments will be made for multiple comparisons. The analysis of our secondary outcomes is mainly hypothesis generating. Additionally, all adverse events will be detailed in a separate table (**Table 4).**

Sensitivity Analysis

We will perform a sensitivity analysis to assess the impact of missing data and multiple imputation, by performing the analysis of the primary outcome including complete cases only and comparing this analysis with our analysis outlined above (i.e., using multiple imputation).

Subgroup Analyses

In our original NO PAin protocol[2], we pre-specified three subgroup analyses, comparing:

1) Shoulder versus knee arthroscopy patients – Hypothesis: the intervention will be more effective among patients undergoing knee arthroscopy versus shoulder arthroscopy, as the latter is typically considered to be a more painful procedure.

2) Patients who received a regional block of any kind as part of their anaesthetic versus those who did not – Hypothesis: the intervention will be more effective among patients receiving a regional block, as they can be expected to experience less pain overall.

3) Males versus females – Hypothesis: the intervention will be more effective among male patients, as they are at higher risk of opioid overuse following a surgical procedure[3].

These subgroup analyses will be performed as a linear regression of the primary outcome, including treatment by subgroup interactions to assess whether the magnitude of the treatment effect is significantly different between these subgroups (**Figure 1**).

PROPOSED TABLES AND FIGURES

Table 1. Patient Demographics

Characteristics	Treatment A N=	Treatment B N=	Total N=
Age, mean (SD)			
Sex, n (%) Males Females			
BMI, n (%) Underweight <18.5 Normal weight 18.5 to <25 Overweight 25 to <30 Obese 30 to <40 Morbidly obese ≥40			
Use of Tobacco Products, n (%) No Yes Yes, quit			
Alcohol Consumption, n (%) No alcohol at baseline Yes, < 5 drinks/week Yes, > 5 drinks/week			
Sport Activity Level, n (%) None Light Moderate			
Co-morbidities, n (%) Osteopenia Osteoporosis Lung disease Asthma Etc… (add based on data)			
Employment Status, n (%) Employed Not employed, retired Not employed, other			
Type of Injury, n (%) Knee Shoulder			

Table 2. Surgical Details

Variable	Treatment A N=	Treatment B N=	Total N=
Operative Joint, n (%) Knee Shoulder			
Side, n (%) Right Left			
Knee Procedures Performed, n (%) ACL reconstruction (+/- LET) MPFL reconstruction (not including TTO)			

Variable	Treatment A N=	Treatment B N=	Total N=
Chondroplasty Meniscectomy Meniscal repair Meniscal transplant Microfracture Autologous Chondrocyte Implantation Osteochondral lesion fixation Irrigation and/or debridement Loose body removal Synovectomy Etc… (add based on data)			
Shoulder Procedures Performed, n (%) Subacromial decompression Rotator cuff repair Shoulder stabilization Superior capsular reconstruction Biceps tenotomy/tenodesis Capsular release SLAP repair Diagnostic arthroscopy Irrigation and/or debridement Loose body removal Synovectomy Etc… (add based on data)			
Anesthetic Strategy, n (%) General Anesthetic Spinal Anesthetic **Regional Block, n (%)** Yes No			

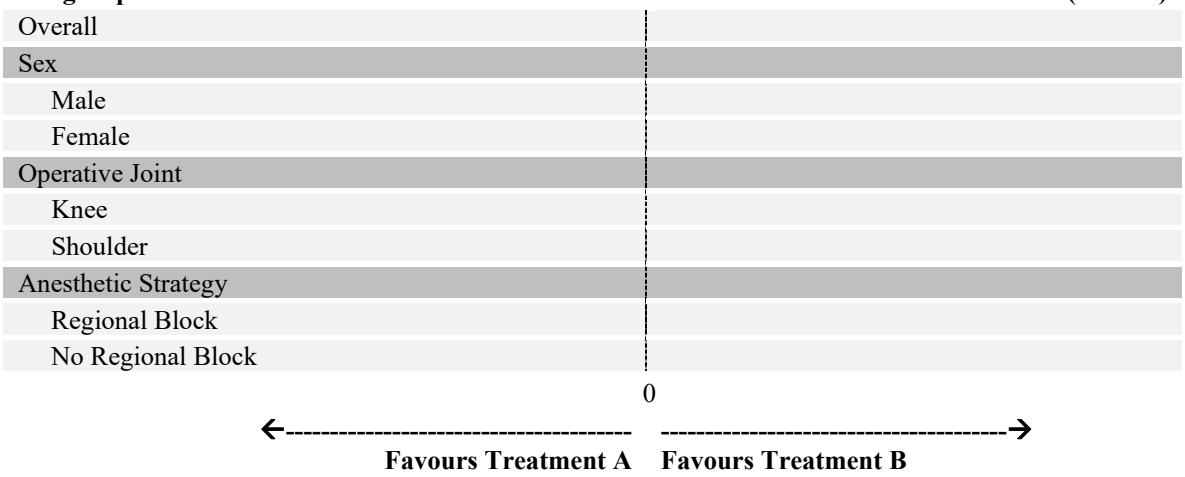
Table 3. Study Outcomes by Treatment Group

	Total N=	Treatment A N=	Treatment B N=	Mean Difference* (95% CI)	p-value
	mean (SD)	mean (SD)	mean (SD)		
Primary Outcome (Total OMEs consumed)					
Secondary Outcomes					
Patient-reported pain (VAS)					
OMEs prescribed					
	n (%)	n (%)	n (%)	Odds Ratio** (95% CI)	p-value
Patient-reported satisfaction **Satisfied** ("Always", "Usually") **Unsatisfied** ("Sometimes", "Never")					
Opioid Refill Request completed					
Any Adverse Events					

Table 4. Adverse Events

	Treatment A N (%)	Treatment B N (%)	Total N (%)
Deep vein thrombosis Calf swelling and leg pain Adhesive Capsulitis Baker's Cyst Etc… (add based on data)			

Figure 1. Subgroup Analyses of the Primary End Point, According to Treatment Group



Appendix 1 – Oral Morphine Equivalents (OMEs) Conversion Chart (Adapted from Centers for Disease Control)[1]

Opioid	Conversion Factor
Codeine	0.15
Hydrocodone	1
Hydromorphone	4
Morphine	1
Oxycodone	1.5
Oxymorphone	3

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Analyzing Prescription Data and Morphine Milligram Equivalents (MME). *Data Resour | Drug Overdose | CDC Inj Cent*. 2019.
2. NO PAin Investigators. Protocol for a multicenter randomized controlled trial comparing a non-opioid prescription to the standard of care for pain control following arthroscopic knee and shoulder surgery. BMC Musculoskelet Disord. 2021 May 22;22(1):471.
3. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med. 2016 Sep 1;176(9):1286-93.