Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial with a nested qualitative study

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DEDICATION

I would like to dedicate this thesis to my late father, a physician in Vietnam who dreamed of continuing his career as a researcher and writer in Canada. You are my inspiration and all-time role model. Thank you for your relentless hard work, endless sacrifices, unwavering commitment, and lifetime of dedication to better the lives of others, especially my siblings and I, your family, colleagues, and patients.

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PREFACE

This thesis is organized in a manuscript-based format and is comprised of two unique manuscripts. The first manuscript was presented as a podium presentation at the SAGES 2021 Annual Congress and was submitted for publication in JAMA Network Open in February 2022. The second manuscript was presented as a podium presentation at the SAGES 2022 Annual Congress and was submitted for publication in Surgical Endoscopy in March 2022.

ABSTRACT

Background

Overprescribing opioids to surgical patients is recognized as an important contributor to the opioid crisis. However, the value of prescribing opioid analgesia (OA) versus opioid-free analgesia (OFA) after postoperative discharge remains uncertain. The overarching aim of this thesis is to lay the groundwork for future trials aimed to address this knowledge gap and contribute preliminary evidence regarding the effectiveness and safety of post-discharge OFA after outpatient general surgery.

Methods

This thesis project was conducted in two parts:

Part 1 (Manuscript 1): A pilot study was conducted to investigate the feasibility of conducting a full-scale randomized controlled trial (RCT) to assess the comparative-effectiveness of OA versus OFA after outpatient general surgery. Patients undergoing outpatient abdominal and breast procedures were randomized to receive OA (around-the-clock non-opioids and opioids for breakthrough pain) or OFA (around-the-clock non-opioids and increasing doses and/or adding non-opioid medications if breakthrough pain). Primary outcomes were *a priori* RCT feasibility criteria (i.e., rates of eligibility, consent, randomization, and lost to follow-up). Secondary outcomes included pain intensity and interference, analgesic intake, 30-day unplanned healthcare utilization, and adverse events. Data were analyzed using descriptive statistics and exploratory effect-estimates.

Part 2 (Manuscript 2): To further refine the design of a future full-scale RCT, a nested qualitative study was conducted to explore patients' and clinicians' perspectives and experiences with the pilot trial. A maximum variation sampling method was used to recruit patients and clinicians with diverse characteristics. Semi-structured interviews were conducted to elicit personal perspectives and experiences with the trial interventions and procedures. Interviews were transcribed verbatim and assessed using inductive thematic analysis.

Results

Part 1 (Manuscript 1): A total of 76 patients (39 OA and 37 OFA) were included in the intention-to-treat analysis [mean age 55.5, 66% female, 53% abdominal surgery, 47% breast surgery]. All of the RCT feasibility criteria were achieved. Postoperative pain intensity and interference were comparable between groups. Twenty-two patients (56%) randomized to OA did not take opioids. One patient (3%) randomized to OFA received an opioid prescription. Common adverse events included constipation (OA 41% vs. OFA 32%) and nausea (21% vs. 16%). Unplanned healthcare utilization was required by 6 patients in the OA group (15%) and 1 patient in the OFA group (3%).

Part 2 (Manuscript 2): Ten patients (5 abdominal, 5 breast) and 10 clinicians (6 surgeons, 2 anesthesiologists, 2 nurses) were interviewed. Five major themes emerged: readiness for trial engagement, pre-trial thoughts about the interventions, postoperative pain experiences, intervention acceptability, and trial refinement. Most patients were open to OFA. Clinicians expressed willingness to prescribe OFA, particularly after less invasive procedures and when using peripheral nerve blocks (PNBs). Concerns were raised regarding the adequacy of pain control and side-effects of non-opioid drugs (e.g., NSAID-induced bleeding, kidney injury). Overall, participants were enthusiastic about the trial and recognized its relevance; clinicians praised the study design and organization, and patients valued the use of electronic questionnaires.

Suggestions for improvements included preventing potential bias arising from the use of PNBs (i.e., via standardization or stratification) and reducing patient burden (i.e., decreasing postoperative questionnaires).

Conclusions

The research reported in this thesis contributes preliminary comparative-effectiveness data and supports the feasibility of conducting a robust full-scale RCT comparing post-discharge OA versus OFA after outpatient general surgery. Lessons learned from patients and clinicians will be used to optimize trial design to better inform evidence-based postoperative pain management. This thesis contributes an essential first step for building a strong body of evidence to mitigate the negative downstream effects of opioid overprescribing after surgery.

RÉSUMÉ

Contexte

La prescription excessive postopératoire d'opioïdes est reconnue comme un contributeur important à la crise des opioïdes. Cependant, la valeur de la prescription des analgésiques opioïdes (OA) par rapport aux analgésiques sans opioïdes (OFA) après la sortie postopératoire reste incertaine. L'objectif principal de cette thèse est de bâtir une base pour les futurs essais visant à combler ce manque de connaissances et à contribuer des preuves préliminaires concernant l'efficacité et l'innocuité des OFA après la sortie d'une chirurgie générale ambulatoire.

Méthodes

Ce projet de thèse s'est déroulé en deux parties :

Partie 1 (Manuscrit 1) : Une étude pilote a été menée pour étudier la faisabilité de mener un essai contrôlé randomisé (ECR) à grande échelle pour évaluer l'efficacité comparative de l'OA par rapport à l'OFA après une chirurgie générale ambulatoire. Les patients subissant des procédures abdominales et mammaires ambulatoires ont été randomisés pour recevoir OA ou OFA. Les résultats d'interêts primaires étaient les critères de faisabilité a priori des ECR. Les résultats d'interêts secondaires comprenaient l'intensité et l'interférence de la douleur, la prise d'analgésiques, l'utilisation non planifiée des soins de santé sur 30 jours et les événements indésirables. Les données ont été analysées à l'aide de statistiques descriptives et d'estimations exploratoires des effets.

Partie 2 *(Manuscrit 2) :* Une étude qualitative imbriquée a été menée pour explorer les perspectives et les expériences des patients et des cliniciens avec l'essai pilote. Une méthode d'échantillonnage

à variation maximale a été utilisée pour recruter des patients et des cliniciens présentant diverses caractéristiques. Des entretiens semi-structurés ont été menés pour obtenir des perspectives et des expériences personnelles avec les interventions et les procédures de l'essai. Les entretiens ont été retranscrits textuellement et évalués à l'aide d'une analyse thématique inductive.

Résultats

Partie 1 (Manuscrit 1) : 76 patients (39 OA et 37 OFA) ont été inclus dans l'analyse en intention de traiter [âge moyen 55,5 ans, 66 % de femmes, 53 % chirurgie abdominale, 47 % chirurgie mammaire]. Tous les critères de compétence de l'ECR ont été obtenus. L'intensité et l'interférence de la douleur postopératoire étaient comparables entre les groupes. Vingt-deux patients (56 %) randomisés pour l'OA n'ont pas pris d'opioïdes. Un patient (3 %) randomisé dans l'OFA a reçu une prescription d'opioïdes. L'utilisation non planifiée des soins de santé a été requise par 6 patients du groupe OA (15 %) et 1 patient du groupe OFA (3 %). Les événements indésirables courants étaient la constipation (41 % contre 32 %) et les nausées (OA 21 % contre OFA 16 %).

Partie 2 (Manuscrit 2) : Dix patients (5 abdominaux, 5 mammaires) et 10 cliniciens (6 chirurgiens, 2 anesthésistes, 2 infirmiers) ont été interrogés. Cinq thèmes majeurs ont émergé : la préparation à l'engagement dans l'essai, les réflexions avant l'essai sur les interventions, les expériences de douleur postopératoire, l'acceptabilité de l'intervention et le raffinement de l'essai. La plupart des patients étaient ouverts à l'OFA. Les cliniciens ont exprimé leur volonté de prescrire l'OFA, en particulier après des procédures moins invasives et lors de l'utilisation de blocs nerveux périphériques (PNB). Des inquiétudes ont été posées concernant l'adéquation du contrôle de la douleur et les effets secondaires des médicaments non opioïdes (par exemple, provoqués par les AINS, lésions rénales). En général, les participants étaient enthousiastes à propos de l'essai et ont reconnu sa pertinence ; les cliniciens ont loué la conception et l'organisation de l'étude, et les

patients ont apprécié l'utilisation des questionnaires électroniques. Les suggestions d'amélioration comprenaient la prévention des biais potentiels entraînant de l'utilisation des PNB (c'est-à-dire via la normalisation ou la stratification) et la réduction du fardeau du patient (c'est-à-dire la diminution des questionnaires postopératoires).

Conclusion

La recherche décrite dans cette thèse apporte des données préliminaires d'efficacité comparative et soutient la faisabilité de mener un solide ECR à grande échelle comparant l'OA post-congé à l'OFA après une chirurgie générale ambulatoire. Les leçons apprises des patients et des cliniciens seront utilisées pour optimiser la conception des essais afin de mieux éclairer la gestion de la douleur postopératoire fondée sur des données probantes. Cette thèse constitue une première étape essentielle pour la constitution d'un solide corpus de preuves visant à atténuer les effets négatifs en aval de la prescription excessive d'opioïdes après une intervention chirurgicale.

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CONTRIBUTION OF AUTHORS

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Author of this thesis, principal author of manuscript I and II, involved in all stages of the research presented (study design, project coordination, data collection, analysis, and interpretation).

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LIST OF PUBLICATIONS AND CONFERENCE PRESENTATIONS

Publications

1. Fiore JF, Jr., El-Kefraoui C, Chay MA, Nguyen-Powanda P, **Do U,** Olleik G, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised trials. *Lancet.* In press.
2. **Do U**, Pook M, Najafi T, Rajabiyazdi F, El-Kefraoui C, Balvardi S, et al. Opioid-free analgesia after outpatient general surgery: A qualitative study focused on the perspectives of patients and clinicians involved in a pilot trial. *Surg. Endosc.* Submitted for publication.
3. **Do U**, El-Kefraoui C, Pook M, Balvardi S, Barone N, Nguyen-Powanda P, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. *JAMA Netw. Open*. Under Review.
4. El-Kefraoui C, Olleik G, Chay MA, Kouyoumdjian A, Nguyen-Powanda P, Rajabiyazdi F, **Do U**, et al. Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis. *BMJ Open*. 2020;10(1): e035443. https://doi.org/10.1136/bmjopen-2019-035443

Presentations

1. **Do U,** Pook M, Najafi T, et al. Opioid-free analgesia after outpatient general surgery: A qualitative study focused on the perspectives of patients and clinicians involved in a pilot trial. Podium presentation at Society of American Gastrointestinal and Endoscopic Surgeons 2022 Annual Congress; March 2022; Denver, CO.
2. El-Kefraoui C, Chay MA, Nguyen-Powanda P, **Do U,** Olleik G, et al. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta- analysis of randomised controlled trials. Poster presentation at 26th Annual McGill Pain Day; January 2022; Montreal, QC. (First place Human/Clinical poster presentation).
3. **Do U**, El-Kefraoui C, Pook M, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Poster presentation at 26th Annual McGill Pain Day; January 2022; Montreal, QC. (Third place Human/Clinical poster presentation).
4. **Do U,** Pook M, Najafi T, et al. Opioid-free analgesia after outpatient general surgery: A qualitative study focused on the perspectives of patients and clinicians involved in a pilot

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5. **Do U**, El-Kefraoui C, Pook M, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Podium presentation at Canadian Surgery Forum 2021 Annual Meeting; September 2021; Halifax, NS. Abstract available at: https://www.canjsurg.ca/content/64/6_Suppl_2/S80
6. **Do U**, El-Kefraoui C, Pook M, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Podium presentation at Society of American Gastrointestinal and Endoscopic Surgeons 2021 Annual Congress; September 2021; Las Vegas, NV. Abstract available at: *Surg Endosc* **35**, 1–103 (2021). https://doi.org/10.1007/s00464-021-08747-w
7. **Do U**, El-Kefraoui C, Pook M, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Poster presentation at 31st Annual Fraser N. Gurd Surgical Research Forum; May 2021; Montreal, QC.
8. Di Lena E, Antoun A, Barone N, **Do U,** Meterissian S. Sentinel lymph node biopsy in women over 70 – Evaluation of rates of axillary staging and impact on adjuvant therapy in elderly women. Podium presentation at Canadian Society of Surgical Oncology 2021 Annual Meeting; May 2021; Toronto, ON.
9. **Do U**, El-Kefraoui C, Pook M, et al. Opioid-free analgesia after hospital discharge following outpatient general surgery: A pilot randomized controlled trial. Poster presentation at 21st Annual Minimally Invasive Surgery Day; November 2020; Montreal, QC.
10. El-Kefraoui C, Olleik G, Chay MA, Kouyoumdjian A, Nguyen-Powanda P, Rajabiyazdi F, **Do U**, et al. Opioid versus opioid-free analgesia after surgical discharge: protocol for a systematic review and meta-analysis. Poster presentation at Experimental Surgery 2019 Research Day; November 2019; Montreal, QC. (First place poster presentation)

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LIST OF ABBREVIATIONS

ASA: American Society of Anesthesiology

ATC: Around-the-clock

BMI: Body Mass Index

BPI-SF: Brief Pain Inventory Short-Form

CI: Confidence Interval

CONSORT: Consolidated Standards of Reporting Trials

COREQ: Consolidated Criteria for Reporting Qualitative Studies

COVID-19: Coronavirus Disease 2019

COX-2: Cyclooxygenase-2

CSF: Canadian Surgery Forum

DSQ: Dossier Santé Québec

ED: Emergency Department

EMR: Electronic Medical Records

IQR: Interquartile Range

MBOP: McGill Better Opioid Prescribing

MedDRA: Medical Dictionary for Regulatory Activities

MME: Morphine Milligram Equivalents

MUHC: McGill University Health Centre

NSAID: Non-Steroidal Anti-Inflammatory Drug

OA: Opioid Analgesia

OFA: Opioid-Free Analgesia

OR: Operating Room

OR-SDS: Opioid-Related Symptom Distress Scale

PACU: Post Anesthesia Recovery Unit

POD: Postoperative Day

POM: Postoperative Month

POMI: Prescription Opioid Misuse Index

POW: Postoperative Week

PRN: Pro re nata; taken as needed

PROMIS-29: Patient-Reported Outcomes Measurement Information System 29 Profile

RCT: Randomized Controlled Trial

REB: Research Ethics Board

SAGES: Society of American Gastrointestinal and Endoscopic Surgeons

SD: Standard deviation

SOAPP: Screener and Opioid Assessment for Patients with Pain

WHO: World Health Organization

CHAPTER 1

INTRODUCTION

1. Opioid analgesics

Opioids are a class of pain-relieving medication (analgesic agent), derived from opium or synthetically derived analogues, that work by binding to opioid receptors (mu, delta, kappa) on neuronal cell membranes.[1,2] When these interactions happen, pain signals from the body are intercepted from reaching the nervous system and consequently, the perception of pain is dampened.[1] Aside from modulating the pain pathway, opioid receptors are also present in regions of the brain associated with the reward pathway whereby the binding of opioids can induce a state of euphoria, which makes patients at risk for misuse (i.e., the use of substances in a way that they are not intended to be used) and addiction (i.e., the compulsive use of substances despite their harmful consequences).[3,4] Opioids can be classified in several ways, including their mode of synthesis into alkaloids (i.e., naturally derived or synthetic compounds) or by their analgesic strength.[5,6] Opioid analgesic strength is determined by the amount (in comparison to morphine) needed to produce a desirable pain-relieving effect.[6] Strong opioids (e.g., oxycodone, hydromorphone) are more potent than morphine, whereas weaker opioids (e.g., codeine, tramadol) are less potent and typically prescribed in higher doses than morphine.[6] While opioid medications are a mainstay treatment for acute pain after surgery, their use is associated with a variety of potential side-effects including dizziness, nausea, vomiting, constipation, sedation, and respiratory depression.[7] Given the current opioids crisis in North America, risk of opioid misuse, addiction and overdose are also relevant clinical concerns when prescribing opioids to manage postoperative pain.[4,8]

2. The North American Opioid Crisis

North America is in the midst of a crisis of opioid addiction and overdose.[9,10] The overprescription of opioids by clinicians has been identified as a driving force behind the growing number of opioid-related deaths in Canada and the United States. In 2019, 3,668 opioid-related deaths occurred across Canada.[11] In the same year, opioids were involved in nearly 50,000 drug overdose deaths in the United States.[12] Additionally, rates of opioid-related morbidity and mortality have increased significantly during the COVID-19 pandemic.[13,14] In 2020, almost 69,000 opioid-related deaths were recorded in the United States and more than 6,200 in Canada representing, respectively, a 30% and 67% increase compared to 2019.[11,15] Increasing rates of opioid-related overdose and deaths during the COVID-19 pandemic may be attributed to disrupted harm reduction services with reduced access to life-saving treatments (i.e., naloxone), lack of social support, and exacerbated mental health challenges due to physical distancing and other public health measures implemented during the pandemic.[16] Importantly, the opioid crisis has also been associated with substantial economic burden. When accounting for healthcare, justice, lost labour productivity, and other direct costs, the estimated economic burden of opioid misuse tops $3.5 billion in Canada and $78.5 billion in the United States, annually.[17,18] In response to this grim statistic, the Canadian and American federal governments have deemed combatting the 'opioid crisis' a top priority.[19,20]

3. Opioid prescribing after outpatient surgery

Surgery often serves as the initial event for opioid-naïve patients to obtain a prescription for opioids and spiral into misuse and addiction.[21,22] Those undergoing outpatient surgery (i.e., a surgical procedure with planned same-day discharge), which represents nearly 80% of all surgeries performed in North America are particularly vulnerable as they invariably require pain medications to be taken at home during the first postoperative days.[23] In North America, analgesia

for these patients often includes over-the-counter non-opioid drugs [e.g., acetaminophen and/or non-steroid anti-inflammatory drugs (NSAIDs)/Cox-2 inhibitors (COX-2)] and prescription opioid tablets to be taken 'as needed' in case of breakthrough pain.[24] With these current prescription pattern, approximately 6% of opioid-naïve surgical patients become persistent opioid users postoperatively (i.e., they continue to take the drug for more than three months after surgery),[25,26] which may lead to increased risk of opioid addiction and overdose.[27]

Surgical patients who do not become persistent users may also contribute to the opioid epidemic by diverting unused tablets for nonmedical use by others. Of all the opioid tablets prescribed to surgical patients, 42% to 71% go unused.[28] In other words, they are prescribed unnecessarily and become a readily available source for diversion. This is particularly important since, it is estimated that over 50% of people who abuse opioids obtain the drug from friends or relatives with an unused prescriptions.[29]

Although prescribing opioids after outpatient surgery stems from well-intentioned efforts to reduce patients' postoperative pain and discomfort, postoperative opioid overprescribing is an urgent element of the opioid crisis given how commonly it may contribute to misuse, diversion, addiction, and death.[30]

4. Preventing opioid prescribing after outpatient surgery

Recent literature suggests that, to prevent postoperative opioid-related harms, surgeons may consider prescribing only non-opioid drugs to manage pain after hospital discharge.[31-33] In many European, Asian, and South African countries, less than 5% of postoperative discharge prescriptions include opioids, whereas more than 80% of patients in North America are prescribed opioids postoperatively.[34-37] Interestingly, pain-related outcomes (i.e., adverse events, satisfaction

with pain treatment) in these countries are often superior to North America.[38-45] These findings support that the decision to prescribe opioids at postoperative discharge largely depends on surgeons' preference and healthcare culture; hence, there is an urgent need for robust comparative-effectiveness trials to guide prescription decision-making.

Currently, studies investigating the comparative-effectiveness of opioid analgesia (OA) versus opioid-free analgesia (OFA) are heterogenous and sparse. In 2019, Fiore et al. conducted a scoping review to systematically map the extent, range and nature of the literature addressing postoperative opioid-free analgesia.[46] Results from this review showed that there is a limited number of studies addressing OFA after hospital discharge (n=46), with only 8 randomized controlled trials (RCTs) comparing post-discharge OFA to OA. Among these RCTs, only 4 involved patients undergoing outpatient general surgery.[46] However, these trials were small in size (n<150) and focused on the comparative-effectiveness of weak opioids (codeine) prescribed around-the-clock.[38,43,44] This does not reflect current prescription patterns in North America where patients are typically prescribed stronger opioids (i.e., oxycodone, hydrocodone) and are instructed to take these drugs 'as needed' in case of breakthrough pain.[47,48] Moreover, evidence regarding the benefits of postoperative opioids has largely relied on unimodal (i.e., using only one type of medication for pain relief), single-dose studies conducted for regulatory purposes under strict experimental conditions.[49] Arguably, a more appropriate approach to guide clinical practice is to examine the impact of postoperative opioids in 'real-world' conditions, where analgesia strategies are often multimodal (i.e., combining various groups of medications for pain relief) and pain treatment spans several days.[49]

A recent meta-analysis completed by our research group suggested that multi-dose opioid prescribing at surgical discharge does not reduce pain intensity but does increase adverse events.[50]

However, data were largely derived from low quality trials (due to non-compliance with intention-to-treat principle, poor description of the randomization process, and potential selective reporting), supporting that there is a great need to advance the quality of research in this field.

5. Feasibility and acceptability of an RCT involving opioid-free analgesia

Given the rationale and evidence reported above, there is an urgent need for robust RCTs focused on the comparative-effectiveness of OA versus OFA after outpatient surgery. Randomized controlled trials are considered to provide the most rigorous method for hypothesis testing and are regarded as the gold standard to evaluate the comparative-effectiveness of different treatments.[51,52] The main advantages of RCTs in comparison to other research methods (i.e., observational studies) are that it rigorously minimizes many sources of bias (i.e., selection bias and confounders).[51] Randomization ensures that each patient enrolled in a trial has an equal chance of receiving the treatments under study, which generates intervention groups that are alike in all relevant factors that may influence outcomes, except for the intervention.[53] Therefore, any observed differences in outcome are more likely to be due to the intervention rather than any other factor.[53] However, undertaking a RCT involving OFA raises important practical concerns including surgeon and patient hesitation about pain treatment without opioids, randomization approach, compliance with treatment allocation, and optimal outcome measurement strategy. Due to the complexity inherent to well-designed RCTs, feasibility studies are a critical first step to assess acceptability, test logistical needs, optimize trial design, and inform the capacities required for a full-scale trial.[54]

Currently, little is known about North American clinicians' and patients' expectations and receptiveness to opioid-free postoperative recovery. As prescribing opioids to manage pain after discharge is embedded in North America's healthcare culture, some surgeons may be hesitant to discharge patients without an opioid prescription, anticipating a negative impact of opioid-free

analgesia on pain outcomes. Similarly, some patients may be doubtful about the efficacy of pain treatment without opioids and refuse trial participation. Given that preconceived notions and beliefs about novel treatments may influence treatment response and adherence, it is crucial to explore patients' and clinicians' expectations and experiences with OFA following outpatient surgery.[55]

6. Thesis objectives

In light of the research gaps described above, the overarching objective of this thesis project is to lay the groundwork for future high-quality trials addressing the comparative-effectiveness of OA versus OFA after outpatient general surgery.

The specific research aims were to:

1) Investigate the feasibility of conducting a full-scale RCT to assess the comparative-effectiveness of post-discharge OA versus OFA after outpatient general surgery.

2) Explore patients' and clinicians' perspectives and experiences with a pilot RCT focused on OA versus OFA after outpatient general surgery.

Given the nature of the studies conducted, this thesis has been divided into two manuscripts. The first manuscript (focused on objective 1) reports the quantitative analysis of our pilot RCT, including feasibility outcomes and exploratory analysis of patients' postoperative outcomes. The second manuscript (focused on objective 2) reports our qualitative study focused on interviews with patients' and clinicians' involved in the pilot trial. The results reported in both manuscrips will inform the planning of a future full-scale, definitive RCT on post-dicharge OA versus OFA after outpatient general surgery.

CHAPTER 2

MANUSCRIPT 1 – Submitted to JAMA Network Open (February 2022)

Opioid-free analgesia after hospital discharge following outpatient general surgery: A Pilot Randomized Controlled Trial.

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2.1 ABSTRACT

Background

The value of prescribing OA versus OFA after postoperative discharge remains uncertain. This study investigated the feasibility of conducting a full-scale RCT to assess the comparative-effectiveness of opioid analgesia (OA) versus opioid-free analgesia (OFA) after outpatient general surgery.

Methods

In this pilot RCT, adult patients undergoing outpatient abdominal and breast surgeries were randomized to receive OA (around-the-clock non-opioids and opioids for breakthrough pain) or OFA (around-the-clock non-opioids and increasing doses and/or adding non-opioid medications if breakthrough pain). Primary outcomes were a priori RCT feasibility criteria. Secondary outcomes included pain intensity and interference, analgesic intake, 30-day unplanned healthcare utilization, and adverse events. Data were analyzed using descriptive statistics and exploratory effect-estimates.

Results

A total of 76 patients (39 OA and 37 OFA) were included in the intention-to-treat analysis [mean age 55.5, 66% female, 53% abdominal surgery, 47% breast surgery]. All the RCT feasibility criteria were fulfilled. Postoperative pain intensity and interference were comparable between groups. Twenty-two patients (56%) randomized to OA did not take opioids. One patient (3%) randomized to OFA received an opioid prescription. Unplanned healthcare utilization was required

by 6 patients in the OA group (15%) and 1 patient in the OFA group (3%). Common adverse events were constipation (OA 41% vs. OA 32%) and nausea (21% vs. 16%).

Conclusions

This pilot trial contributes preliminary comparative-effectiveness data and supports the feasibility of conducting a robust full-scale RCT to inform evidence-based analgesia prescribing after outpatient general surgery.

Keywords

Analgesia; feasibility; opioids; opioid-free; outpatient surgery; postoperative; randomized controlled trial

2.2 INTRODUCTION

The overprescription of opioids by surgeons is recognized as a contributor to the current opioid crisis.[56,57] Recent literature suggests that, to prevent opioid-related harms after outpatient general surgery, clinicians may consider prescribing only non-opioid drugs to manage pain after postoperative discharge.[32,33] However, while this practice is common in some countries,[37,58] evidence regarding the comparative-effectiveness of opioid versus opioid-free analgesia remains uncertain. Findings from a recent scoping review support that the number of randomized clinical trials (RCTs) in this field is limited,[46] whilst existing small trials often challenged the value of prescribing opioids for post-discharge analgesia.[38,43,44] Lack of evidence in this field means the decision to prescribe opioids largely depends on surgeons' preference and healthcare culture; hence, there is an urgent need for robust RCTs to guide clinical decision-making.

Due to the complexity inherent in well-designed RCTs, pilot studies are a critical first step to assess acceptability, test logistical needs, optimize design, and inform the capacities required for a full-scale trial.[54] Undertaking a RCT with opioid-free analgesia raises important practical concerns including surgeon and patient hesitation about pain treatment without opioids, randomization approach, adherence, and optimal outcome measurement. Thus, the objective of this pilot study was to investigate the feasibility of conducting a full-scale RCT to assess the comparative-effectiveness of analgesia regimens including opioids (opioid analgesia, OA) versus to opioid-free analgesia (OFA) after outpatient general surgery.

2.3 METHODS

The study was approved by our institutional ethics board (MUHC REB 2020-5965) and all participants provided written informed consent. The protocol, available in Appendix, was

registered *a priori* (ClinicalTrials.gov: NCT04254679). Analysis and reporting followed the CONSORT extension for pilot trials (Appendix Table A1).[59]

2.3.1 Study Design and Patients

This was a parallel, two-group, assessor-blind, pragmatic pilot RCT with participants allocated 1:1 to receive OA or OFA after postoperative discharge. We included adult patients (≥18 years) undergoing abdominal and breast outpatient surgeries at two university-affiliated hospitals. Surgeon agreement to have their patients in the trial was required for inclusion. We excluded patients with contraindications to any of the drugs used in the trial (i.e., substance use disorder, heart failure, allergy, peptic ulcer, bleeding disorders, renal or liver impairment),[60-62] who were taking opioids preoperatively, and with conditions that could interfere with outcome assessment (e.g., cognitive impairment, inability to understand English or French, and limited access to a telephone or computer). Patients were excluded postoperatively if they had intraoperative or early surgical complications requiring hospital stay.

2.3.2 Randomization and Blinding

The random allocation sequence was generated electronically (via www.sealedenvelope.com) by an external researcher not involved in the trial and uploaded onto REDCap (http://project-redcap.org/). Permuted blocks of varying sizes (2, 4, or 6) were used and randomization was stratified by abdominal versus breast surgery. There was no stratification by center as the trial sites were specialized in either procedure type. Randomizations were conducted by research staff present in the OR using the project's REDCap randomization module. Treatment allocations were concealed until patients were deemed ready to be discharged from the operating room (OR) to the post-anesthesia care unit (PACU).

After randomization, patients and surgeons were not blinded to the treatment allocation due to the pragmatic nature of the trial. The primary surgeon was informed about the randomization result in the OR, after skin closure, and provided a discharge analgesia prescription according to group assignment. To prevent performance bias during PACU stay (e.g., OFA patients receiving additional analgesia prior to discharge), the prescription was kept in a sealed opaque envelope until patients were deemed ready to leave the hospital. Outcome assessors were blinded to treatment allocations. Blinding effectiveness was estimated by asking assessors to guess patient's group allocation after the last follow-up assessment. Any inadvertent unblinding was reported.

2.3.3 Interventions

OA group (standard care): Patients received a prescription including around-the-clock non-opioid analgesics (acetaminophen and/or NSAIDs) and a supply of opioids to be used as rescue analgesia for breakthrough pain. Given the pragmatic nature of this trial, the specific OA regimen was determined by the patient's primary surgeon considering the surgical procedure, comorbidities, and patient's preference. The OA strategies currently used at the trial sites are guided by the institutions' pain service team and follow Health Canada standards for safety and efficacy.[63] Examples are described in Figure A1 (Appendix).

OFA group: Patients received a prescription including only around-the-clock non-opioid analgesics (acetaminophen alone and/or NSAIDs). In case of breakthrough pain, rescue analgesia was provided by (1) increasing doses of non-opioid analgesics, (2) adding non-opioid drugs that were not included in the initial regimen, or (3) switching drugs according to single-dose efficacy evidence[49] targeting individual variances in analgesia response.[64] The regimen prescribed was determined by the patient's primary surgeon. Suggested OFA strategies, developed with input

from the institutions' pain service team according to Health Canada standards,[63] are described in Figure A2 (Appendix).

Management of persistent pain

As per standard practice at the trial sites, in case of persistent pain despite the available prescription, patients in the OA group were advised to call the surgeon's office/clinic during working hours (weekdays, 8AM to 4PM) or visit the hospital emergency department (ED, after-hours and weekends) for assessment and potential pain management optimization.

As OFA was new to our institutions, a strategy was implemented to ensure that patients received adequate pain management during the trial. Upon hospital discharge, patients receiving OFA had a backup prescription of opioids faxed to a pharmacy close to their residence. To prevent patients from filling out this prescription 'just in case', they were not informed about the availability of the prescription unless they reported persistent pain via a 'study hotline' available 24/7 (i.e., a dedicated mobile phone kept with study staff). When this line was called, patients were informed about the availability of the opioid prescription.

Other aspects of perioperative care

Surgical techniques and in-hospital anesthesia/analgesia interventions were left to the discretion of the surgeons and anesthesiologists to best reflect routine practice. Any nonpharmacological pain intervention recommended by the medical team (e.g., ice compress, acupuncture, massage) were permitted and recorded.

2.3.4 Measurement Strategy

Patient, surgery, and perioperative care characteristics

Details about patients, surgery, and perioperative care characteristics were obtained from electronic medical records (EMRs). Preoperatively, we also collected self-reported data on pain catastrophizing (Pain Catastrophizing Scale),[65,66] potential for opioid misuse [Screener and Opioid Assessment for Patients with Pain (SOAPP)],[67] preferred treatment group, and expectations for treatment effectiveness. See Table A2 (Appendix) for details about these measures.

Feasibility outcomes (primary)

As a pilot study, this trial primarily focused on *a priori* feasibility outcomes. A full-scale RCT would be deemed feasible if, during the study period:

- ≥ 90% of the surgeons who agree to have their patients randomized complied with the agreement, i.e., not change their minds.
- ≥ 70% of patients undergoing the procedures of interest were eligible to be randomized.
- ≥ 50% of eligible patients agreed to participate in the study and were randomized.
- ≥ 80% of the randomized patients complied with their allocated treatment (i.e., did not receive an opioid prescription if randomized to OFA).
- ≥ 80% of the randomized patients completed outcome assessment at 30-days.
- Among patients who completed outcome assessments, the proportion of missing data was less than 10% (i.e., non-response to questionnaires or specific questionnaire items).

Clinical outcomes (secondary)

Clinical outcomes were assessed secondarily to inform the measurement strategy and sample size requirements for the future full-scale RCT. Our outcome measurement strategy included: the Brief Pain Inventory Short-Form (BPI, domains: pain intensity and pain interference),[68] time to stopping pain medication,[69] Patient-Reported Outcomes Measurement Information System 29 Profile (PROMIS-29, domains: physical function, anxiety, depression, fatigue, sleep disturbance, social roles and activities, pain intensity, and pain interference),[70] Perioperative Opioid-Related Symptom Distress Scale (OR-SDS),[71] Prescription Opioid Misuse Index (POMI),[72] 30-day complications,[73,74] 30-day unplanned healthcare utilization (ED visits, unplanned clinic visits, and/or hospital readmissions), 30-day drug adverse events (identified via OR-SDS, medical records, or MedDRA-classified self-report),[75] and prolonged opioid use (3-month follow-up). See Table A3 (Appendix) for details about these measures.

2.3.5 Data Collection and Follow-up Procedures

Patient-reported outcomes were collected preoperatively (baseline), on postoperative days (POD) 1 to 7 and at weeks 2 (POD 14), 3 (POD 21), and 4 (POD 28) postoperatively. Data collection was via electronic questionnaires distributed using REDCap and completed via smartphone, tablet, or personal computer. Electronic data was transmitted directly to a REDCap database and verified by blinded assessors. Patients also had the option to complete questionnaires via telephone with a blinded assessor. Information regarding 30-day complications and unplanned healthcare utilization were obtained via self-report with EMR confirmation. Information regarding opioid dispensing was monitored for 3 months via a province-wide medical database (Dossier Santé Québec). Treatment adherence was monitored (via the REDCap questionnaires or telephone) by unblinded study staff not involved in outcome assessment.

2.3.6 Sample Size

This pilot trial was not confirmatory; therefore, no formal sample size calculation was conducted. In accordance with previous recommendations that at least 70 measured participants are required to estimate standard deviations with enough precision for future sample size calculations,[76] we aimed to recruit and obtain outcome data from 80 patients (40 per group), allowing for a ~15% attrition rate. This sample size is also in line with recommendations regarding the minimal number of participants required to identify feasibility issues.[77]

2.3.7 Statistical Analysis

Descriptive statistics were used to analyze feasibility outcomes. Between-group comparison of postoperative outcomes followed the intention-to-treat principle and focused on descriptive statistics and exploratory effect-estimates. As this was a pilot trial, no inferential statistics targeting statistical significance were performed.[59] To inform the generalizability of our results, we compared the characteristics of randomized patients versus those who did not consent to randomization. All analyses were performed using Stata version 16 software (StataCorp, USA).

2.4 RESULTS

Recruitment of participants occurred between January 29th and September 3rd, 2020 (last follow-up for self-reported outcomes on October 2nd, 2020). The trial was halted from March 15 to June 1, 2020, due to COVID-19 restrictions. All the surgeons who conducted the eligible surgeries during the study period (n=15) agreed to have their patients recruited and complied with the study procedures. In total, 224 patients were assessed for eligibility, 163 met inclusion criteria (73%), and 93 consented for randomization (57%). The trial flow diagram and patient exclusions (with specific reasons) are shown in Figure 2-1. Five patients were excluded after being randomized (3 developed complications requiring hospital stay, 2 had contraindication to NSAIDs identified after randomization), but no patients in either group withdrew due to lack of treatment efficacy or side-

effects. Overall, 76 patients (39 OA and 37 OFA) were included in the intention-to-treat analysis. The characteristics of randomized patients versus those who did not consent to randomization were similar (Appendix Table A4). Adherence to treatment allocation was 99% (one patient in the OFA received a subsequent opioid prescription). Seventy-three patients completed the 30-day follow-up (96%); rate of missing questionnaires was 1% and rate of missing questionnaire items was 0.1%. Based on these findings, all the *a priori* feasibility criteria set for this pilot trial were fulfilled (Table 2-1). Outcome assessors correctly guessed 49% of the patients' group allocation (no more than expected by chance), which supports blinding effectiveness (Appendix Table A5).

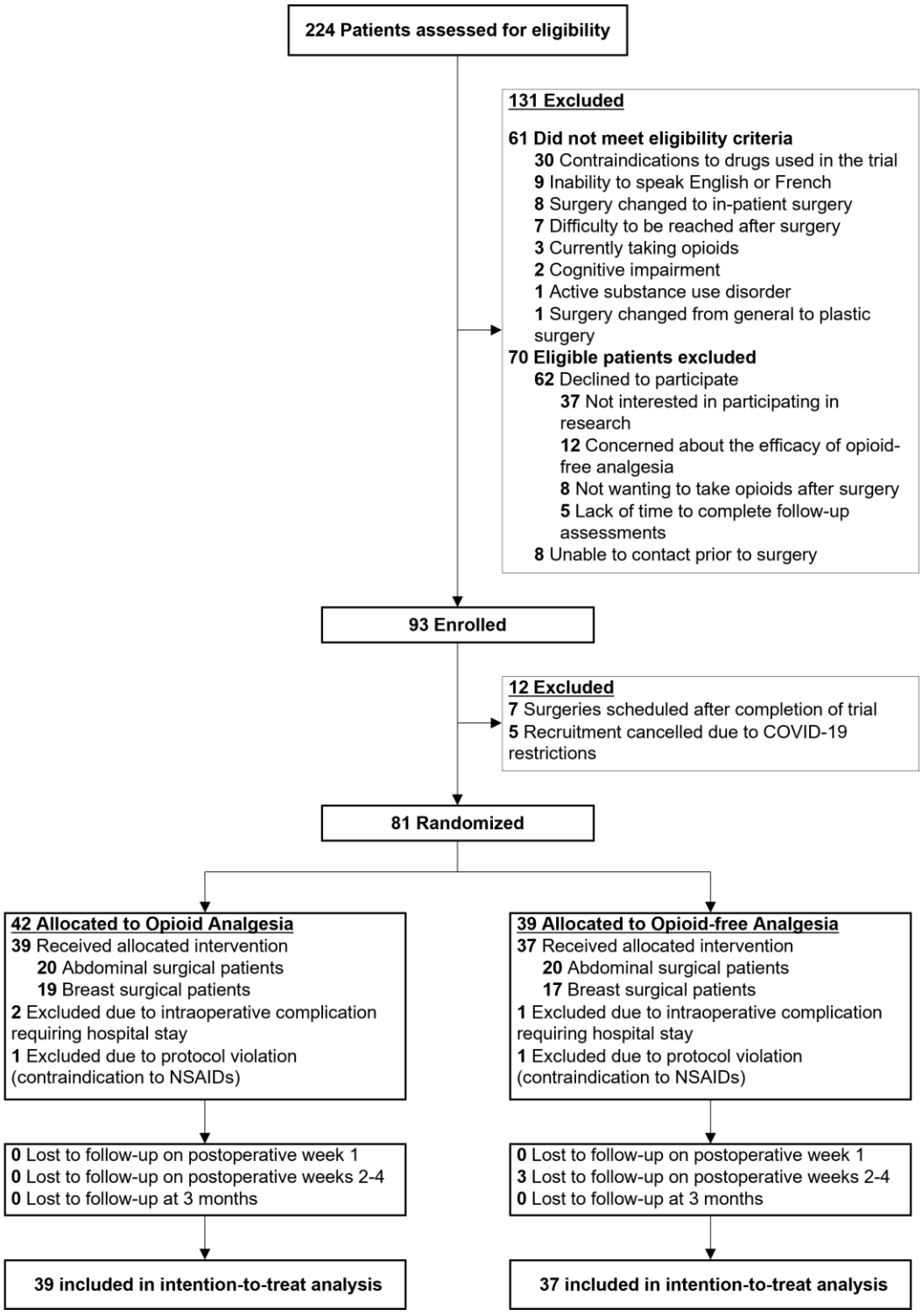


Figure 2-1. CONSORT Diagram
NSAIDs = non-steroidal anti-inflammatory drugs

Table 2-1. Feasibility outcomes

Feasibility criteria	Study findings
≥ 90% of the surgeons agree to have their patients randomized and comply with the agreement	15/15 surgeons (100%)
≥ 70% of screened patients are eligible to be randomized	163/224 patients (73%)
≥ 50% of eligible patients agree to participate in the study	93/168 patients (57%)
≥ 80% of the randomized patients comply with their allocated treatment	75/76 patients (99%)
≥ 80% of the patients randomized complete outcome assessment at 30-days after surgery	73/76 patients (96%)
< 10% of data is missing among patients who complete outcome assessment	37/3724 questionnaires (1%) 33/32256 questionnaire items (0.1%)

Participants' baseline and operative characteristics are reported in Table 2-2. The sample mean age was 55.5 years (range 21-85) and 50 patients (66%) were female. Forty patients (53%) underwent abdominal surgery (48% laparoscopic), and 36 patients (47%) underwent breast surgery (50% with sentinel node biopsy, 16% with axillary node dissection). Prior to randomization, most patients stated preference for being randomized to the OFA group (49%) or had no preference (37%). Most patients expected that OA would be 'very effective' (49%) and OFA would be 'somewhat effective' (37%). The OA and OFA regimens prescribed at discharge are described in Table A6 (Appendix). In the OA group, the average amount of opioids prescribed was 106 MMEs[78] (equivalent to ~14 pills of oxycodone 5mg), 25 patients (64%) filled their opioid prescription, and 17 (44%) reported consuming opioids after discharge. In the OFA group, 8 patients (22%) used the rescue non-opioid analgesia available in their prescription. Only one patient in the OFA group (open inguinal hernia repair) filled an opioid prescription after calling the study hotline due to uncontrolled pain.

Table 2-2. Patient baseline and operative characteristics

	Total (n= 76)	Opioid analgesia (n=39)	Opioid-free analgesia (n=37)
Age, mean (SD), y	55.5 (14.5)	54.3 (15.1)	56.8 (14.0)
≥ 75 years old	5 (7)	2 (5)	3 (8)
Female	50 (66)	24 (61)	26 (70)
BMI, mean (SD)[a]	27.6 (7.0)[g]	26.4 (4.7)[h]	28.8 (8.7)[i]
≥ 30.0	18 (25)[g]	7 (19)[h]	11 (31)[i]
Physical status (ASA), No. (%)			
I	15 (20)	6 (15)	9 (24)
II	53 (70)	25 (64)	28 (76)
III	8 (10)	2 (5)	6 (16)
Risk of opioid abuse score, mean (SD)[b]	1.9 (1.6)	2.0 (1.6)	1.8 (1.7)
Score ≥ 4	9 (12)	4 (10)	5 (14)
Pain catastrophizing score, mean (SD)[c]	13.6 (10.7)	13.5 (10.7)	13.6 (11.0)
Employment, No. (%)			
Employed (including self-employed)	44 (58)	24 (62)	20 (54)
Retired	20 (26)	9 (23)	11 (30)
Homemaker	2 (3)	2 (5)	0 (0)
Student	1 (1)	0 (0)	1 (3)
Unemployed	5 (7)	1 (3)	4 (10)
Unable to work (on disability pension)	4 (5)	3 (8)	1 (3)
Current smoker, No. (%)	13 (18)[h]	8 (21)[i]	5 (14)[i]
Pre-randomization treatment group preference[d], No. (%)			
Unsure or no preference	28 (37)	13 (33)	15 (41)
Opioid medication group	11 (15)	7 (18)	4 (10)
Opioid-free medication group	37 (49)	19 (49)	18 (49)
Pre-randomization perceptions of opioid analgesia[e], No. (%)			
Very effective	37 (49)	17 (44)	20 (54)
Somewhat effective	8 (11)	4 (10)	4 (10)
Not effective	1 (1)	0 (0)	1 (3)
No specific expectation	30 (39)	18 (46)	12 (33)
Prerandomization perceptions of opioid-free analgesia[f], No. (%)			
Very effective	23 (30)	8 (21)	15 (41)
Somewhat effective	28 (37)	17 (44)	11 (30)
Not effective	2 (3)	0 (0)	2 (5)
No specific expectation	23 (30)	14 (35)	9 (24)
Abdominal surgery, No. (%)	40 (53)	20 (51)	20 (54)
Laparoscopic appendectomy	1 (1)	0 (0)	1 (3)
Laparoscopic cholecystectomy	9 (12)	3 (8)	6 (16)
Laparoscopic inguinal hernia repair	9 (12)	8 (21)[j]	1 (3)

	Total (n= 76)	Opioid analgesia (n=39)	Opioid-free analgesia (n=37)
Open inguinal hernia repair	17 (22)	8 (21)	9 (24)
Open umbilical hernia repair	3 (4)	1 (3)	2 (6)
Open incisional hernia repair	1 (1)	0 (0)	1 (3)
Breast surgery, No. (%)	36 (47)	19 (49)	17 (46)
Partial mastectomy	14 (18)	4 (10)	10 (27)
Partial mastectomy with sentinel node biopsy	11 (14)	7 (18)	4 (11)
Partial mastectomy with axillary node dissection	6 (8)	4 (10)	2 (6)
Partial mastectomy with sentinel node biopsy and reconstruction	1 (1)	0 (0)	1 (3)
Total mastectomy with sentinel node biopsy	2 (3)	2 (5)	0 (0)
Total mastectomy with sentinel node biopsy and reconstruction	1 (1)	1 (3)	0 (0)
Total mastectomy with axillary node dissection and reconstruction	1 (1)	1 (3)	0 (0)
Received intraoperative regional analgesia, No. (%)	57 (75)	31 (79)	26 (70)
Peripheral nerve block	11 (14)	5 (13)	6 (16)
Wound infiltration	57 (75)	31 (79)	26 (70)
Duration of surgery, mean (SD) (minutes)	91 (45)	97 (39)	84 (51)
Amount of opioids received in PACU, mean (SD), MME	21 (18)[h]	18 (14)[i]	25 (21)[i]

Data are No. (%), median (IQR), or mean (SD). ASA= American Society of Anesthesiology; BMI=body mass index; MME = Morphine Milligram Equivalent; PACU = Post Anesthesia Care Unit.

[a] Calculated as weight in kilograms divided by square of heights in meters.

[b] Assessed by the Screener and Opioid Assessment for Patients with Pain (SOAPP) Short Form (total score ranges 0-20, score ≥ 4 indicates a likely high risk of opioid abuse after prescription).

[c] Pain catastrophizing assessed by Pain Catastrophizing Scale (recall period not specific, total score ranges 0 = best to 52 = worse).

[d] Patients were asked, "What treatment group do you prefer to be in?"

[e] Patients were asked, "If you are in the group using opioids for pain treatment: What is your expectation of treatment effectiveness?"

[f] Patients were asked, "If you are in the group not using opioids for pain treatment: What is your expectation of treatment effectiveness?"

[g] Missing data for 3 patients.

[h] Missing data for 2 patients.

[i] Missing data for 1 patient.

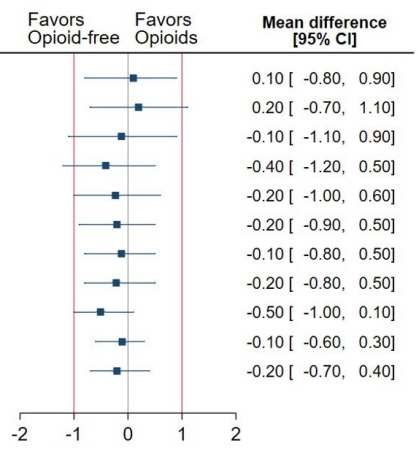
[j] Includes one patient who had an umbilical hernia repair during the same procedure.

Data regarding postoperative pain intensity and interference are reported in Figure 2-2. Assessment of PROMIS-29 domains are reported in Figure A5 (Appendix). Overall, effect estimates and confidence intervals did not capture substantial differences between OA and OFA. Subgroup analyses by surgery type (abdominal and breast) are reported in Figures A6-9 (Appendix).

Satisfaction with pain management and time to stopping pain medication were similar between groups (Table 2-3). One patient was at risk of opioid misuse disorder (POMI score≥2) at 30 days postoperatively. During the 3-month follow-up, four patients filled new opioid prescriptions [OA n=1, OFA n=3, all due to a new surgical procedure (revision of breast resection margin)].

A. Pain intensity

	Opioid-free analgesia					Opioid analgesia				
Timepoint	Mean	SD	Median	IQR	Range	Mean	SD	Median	IQR	Range
Baseline	1.0	2.0	0	[0 - 0]	[0 - 6.8]	0.9	1.7	0	[0 - 0.8]	[0 - 6.5]
POD 1	3.0	1.7	3.0	[2 - 4.3]	[0 - 6.5]	2.8	2.2	3.0	[0.8 - 4.5]	[0 - 8]
POD 2	2.6	2.1	2.0	[0 - 4.3]	[0 - 7.3]	2.7	2.3	2.0	[0.8 - 4.5]	[0 - 7.5]
POD 3	1.7	1.8	1.3	[0 - 3]	[0 - 6.3]	2.1	2.0	1.8	[0 - 3]	[0 - 7]
POD 4	1.4	1.7	1.0	[0 - 2.8]	[0 - 5.5]	1.6	1.7	1.3	[0 - 2.8]	[0 - 6.3]
POD 5	1.1	1.3	0.8	[0 - 2.3]	[0 - 4.3]	1.3	1.7	0.5	[0 - 2]	[0 - 6.8]
POD 6	1.1	1.4	0	[0 - 1.8]	[0 - 5.3]	1.2	1.5	0.3	[0 - 2.5]	[0 - 6]
POD 7	0.9	1.2	0	[0 - 1.8]	[0 - 4.3]	1.1	1.6	0.3	[0 - 2]	[0 - 7.3]
POW 2	0.4	0.8	0	[0 - 0.8]	[0 - 4]	0.9	1.4	0	[0 - 1.5]	[0 - 4]
POW 3	0.4	0.8	0	[0 - 0]	[0 - 3]	0.5	1.0	0	[0 - 0.5]	[0 - 3.5]
POW 4	0.3	0.8	0	[0 - 0]	[0 - 4]	0.5	1.3	0	[0 - 0]	[0 - 7]



B. Pain interference

	Opioid-free analgesia					Opioid analgesia				
Timepoint	Mean	SD	Median	IQR	Range	Mean	SD	Median	IQR	Range
Baseline	0.7	1.7	0	[0 - 0]	[0 - 7]	0.9	1.9	0	[0 - 0]	[0 - 6.1]
POD 1	3.3	2.1	3.4	[1.3 - 4.6]	[0 - 7.3]	3.0	3.1	2.0	[0 - 6.1]	[0 - 8.9]
POD 2	2.3	2.0	2.1	[0 - 3.9]	[0 - 6.7]	2.4	2.5	1.6	[0 - 4.6]	[0 - 8]
POD 3	1.8	1.9	1.7	[0 - 2.4]	[0 - 6.6]	2.1	2.5	1.0	[0 - 4]	[0 - 8.9]
POD 4	1.4	1.9	0.4	[0 - 2]	[0 - 7.6]	1.9	2.6	0.7	[0 - 3.3]	[0 - 10]
POD 5	1.0	1.7	0	[0 - 1.4]	[0 - 7.4]	1.1	1.9	0	[0 - 1.9]	[0 - 7.3]
POD 6	0.8	1.5	0	[0 - 1]	[0 - 6.4]	1.2	2.0	0	[0 - 2.3]	[0 - 7.4]
POD 7	1.0	1.9	0	[0 - 1.1]	[0 - 7.3]	1.1	2.0	0	[0 - 1.1]	[0 - 7.4]
POW 2	0.5	1.5	0	[0 - 0.3]	[0 - 7.6]	1.0	1.7	0	[0 - 1.1]	[0 - 5.9]
POW 3	0.4	1.2	0	[0 - 0]	[0 - 5.9]	0.6	1.5	0	[0 - 0]	[0 - 7]
POW 4	0.1	0.6	0	[0 - 0]	[0 - 3.7]	0.2	0.6	0	[0 - 0]	[0 - 3.1]

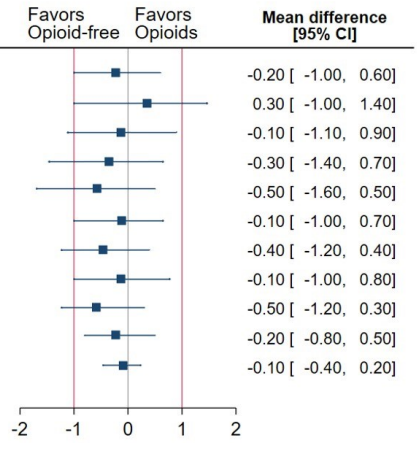


Figure 2-2. Plots represent between-group differences in the Brief Pain Inventory severity scale (composite of 4 items, score 0-10) and interference scale (composite of 7 items, score 0-10).

Red lines represent minimal clinically important differences.[79,80] Missing follow-up data: POW3 n = 2, POW4 n = 3.

Table 2-3. Postoperative outcomes

	Opioid analgesia (n=39)	Opioid-free analgesia (n=37)	Between-group difference (95% CI)[a]
Filled out an opioid prescription, No. (%)[b]			
POW1	25 (64)	1 (3)	-61 (-78.2 to -44.6)
POW2	0 (0)	0 (0)	0 (0 to 0)
POW3	0 (0)	0 (0)	0 (0 to 0)
POW4	0 (0)	0 (0)	0 (0 to 0)
POM2	0 (0)	1 (3)	3 (-2.5 to 7.9)
POM3	1 (3)	2 (6)	3 (-6.1 to 11.7)
Time to stopping pain medications, mean (SD), days[c]	9 (9.0)	9 (7.9)	-1.1 (-4.3 to 3.5)
Medication misuse index score, mean (SD)[d]	0.1 (0.4)	0.1 (0.4)	0 (-0.21 to 0.13)
Score ≥ 2	0 (0)	1 (3)	3 (-2.7 to 8.6)
Satisfied/very satisfied with pain management, No. (%)[e]	37 (95)	34 (92)	-3 (-14.2 to 8.2)
Wished to have received a better pain management strategy, No. (%)[f]	6 (15)	6 (16)	1 (-17.7 to 16.1)
30-day postoperative complications, No. (%)[g]	6 (15)	2 (5)	-10 (-23.4 to 3.4)
Surgical site infection	2 (5)	0 (0)	-5 (-12.1 to 1.8)
Breast hematoma	1 (3)	0 (0)	-3 (-7.5 to 2.4)
Urinary retention	1 (3)	0 (0)	-3 (-7.5 to 2.4)
Neuropathic pain	1 (3)	0 (0)	-3 (-7.5 to 2.4)
Scrotal ecchymosis	1 (3)	0 (0)	-3 (-7.5 to 2.4)
Testicular hematoma	0 (0)	1 (3)	3 (-2.5 to 7.9)
Breast seroma	0 (0)	1 (3)	3 (-2.5 to 7.9)
30-day postoperative complication score (Clavien-Dindo Classification), No. (%)			
I	3 (8)	1 (3)	-5 (-14.9 to 4.9)
II	2 (5)	0 (0)	-5 (-12.1 to 1.8)
IIIa/b	1 (3)	1 (3)	0 (-7.1 to 7.3)
30-day comprehensive complication index, median (IQR)[h]	2.6 (7.2)	0.9 (4.5)	1.7 (-1.1 to 4.4)
30-day unplanned healthcare utilization, No. (%)	6 (15)	1 (3)	-12 (-25.1 to 0.2)
ED visits	5 (13)	0 (0)	-10 (-19.8 to -0.7)
Readmission	1 (3)	1 (3)	0 (-7.2 to 7.9)
Outpatient clinic visit	2 (5)	0 (0)	-5 (-12.1 to 1.8)

Data are No. (%), median (IQR), or mean (SD). CI = confidence interval; ED = emergency department; POD = postoperative day; POM = postoperative month; POW = postoperative week.

[a] Between-group difference indicates mean difference for continuous variables and proportion difference (in percentage) for dichotomous variables.

[b] Data collected from Dossier Santé Québec, missing 1 patient from opioid analgesia group due to restricted access to patient's files.

[c] Time to the first report of stopping the use of pain medication was calculated based on the first of two consecutive reports of 'did not use pain medication' from POD1 until POD7. If analgesia intake continued beyond POD 7, patients were asked to recall the last day of pain medication use at POW2, 3 and 4. For patients who were lost to follow-up (OFA n=3), the last reported dates of medication use were used in the analysis.
[d] Medication misuse index score assessed by the Prescription Opioid Misuse Index (recall period 4 weeks, total score ranges 0-6, score ≥ 2 indicates a likely diagnosis of medication misuse disorder).
[e] Patients were asked, "How satisfied are you with the pain treatment you have received after the operation?" (very dissatisfied/ dissatisfied/satisfied/very satisfied) at POD7.
[f] Patients were asked, "Do you wish that your pain was better managed by the health care team?" (yes/no) at POD7.
[g] Data collected from patient's clinical charts.
[h] range 0-100, higher scores indicate higher severity of complications.

Rates of adverse events identified using the OR-SDS questionnaire are reported in Table A7 (Appendix). Most events were reported within 7 days postoperatively and included constipation (OA 41% vs. OFA 32%), nausea (21% vs. 16%), vomiting (8% vs. 3%), and itching (33% vs. 19%). Other postoperative health issues spontaneously reported by patients included headache (OA 10% vs. OFA 3%), and diarrhea (3% vs. 5%) (Appendix Table A8). Postoperative complications were developed by 6 patients in the OA group (15%) and 2 patients in the OFA group (5%) (Table 2-3). Unplanned healthcare utilization was required by 6 patients in the OA group (15%) and 1 patient in the OFA group (3%)

2.5 DISCUSSION

Findings from this pilot trial support the feasibility of conducting a full-scale RCT to compare OA versus OFA after outpatient general surgery. Overall, the trial proposed was welcomed by all the stakeholders involved (i.e., funders, ethics committee, patients, scientists, surgeons, anesthesiologists, and other perioperative care clinicians), supporting that there is recognition of the uncertainty regarding comparative-effectiveness of OA versus OFA after postoperative discharge.

The most common barrier to participation among eligible patients was no willingness to take part in research while receiving care (58%); however, a considerable proportion of patients (28%) did not consent to randomization because of preconceptions about the use of opioids for postoperative

analgesia. While some patients were concerned about the efficacy of OFA (17%), others did not want to take opioids postoperatively given the risk of addiction and side effects (11%) (Figure 3-1). This finding supports that recruitment for the full-scale trial may be facilitated by addressing implicit biases and emphasizing the equipoise between the two interventions. Interestingly, most patients stated a preference for being randomized to the OFA group (49%) or had no preference (37%) and, among those randomized to OA, only 64% filled their prescription and 44% used opioids after discharge. The latter finding corroborates previous literature showing that a considerable number of opioid pills prescribed to surgical patients go unused.[28] It is important to note that patients' preference for not taking opioids (even when randomized to receive a prescription) is inherent to a pragmatic trial aimed to assess the value of opioid prescribing in real-world settings.

The prescription of opioids to surgical patients often stems from concerns of inadequate pain control after discharge, which may potentially increase emergency visits and readmissions.[31,81] Given this concern, trial participants randomized to the OFA group had a 'study hotline' available to report uncontrolled pain, as well as a backup opioid prescription faxed to their pharmacy. During the study period, only two patients used the study hotline to report uncontrolled pain. One patient ultimately filled the backup opioid prescription, while the other reported improvement after optimizing the dosing of non-opioid drugs (previously taken incorrectly). None of the episodes of unplanned healthcare utilization had 'uncontrolled pain' as the chief complaint. However, it is important to note that the overall rates of the unplanned healthcare utilization tended to be higher in patients randomized to OA (15% vs. 3%). Postoperative complications, which were the main drivers to ED visits and readmissions, also tended to be higher among patients in the OA group (15% vs. 5%). While these findings may have occurred by chance given our low sample size, they warrant further investigation in a full-scale RCT.

A major strength of this pilot trial is its methodological rigour and strict adherence to the CONSORT statement for pilot and feasibility trials.[59] We also ensured *a priori* registration of the study protocol to attest transparency and prevent reporting bias. However, this trial is subject to limitations. Given the pilot nature of the study, in line with CONSORT recommendations,[59] no inferential statistical analyses were performed to compare groups. While we successfully obtained a wide range postoperative outcome data, our study was not statistically powered to detect between-group differences, therefore, any between-group comparison should be interpreted with caution. Our feasibility findings were obtained in two tertiary academic hospitals and may not be generalizable to other centres. Patient recruitment was interrupted for 3 months due to the COVID-19 pandemic; we cannot exclude that widespread social isolation may have impacted some aspects of the trial (i.e., seeking care for potential complications/adverse events). Randomization of patients in the PACU (with discharge prescriptions written right before hospital discharge) would have optimized concealment of allocation but this was considered impractical by surgeons who often write their prescriptions in the OR after skin closure. Two patients were excluded from the trial after randomization because they had contraindications to NSAIDs known by surgeons and anesthetists but not documented in EMRs. This indicates that further screening measures are warranted in the full-scale RCT (i.e., confirming eligibility with the medical team prior to randomization). An ongoing qualitative study involving perioperative care clinicians and patients who took part in the trial will further elucidate challenges and mitigation strategies, as well as assist the selection of primary outcomes to inform sample size calculation for the future full-scale RCT.

2.6 CONCLUSION

The overprescription of opioids postoperatively is recognized as a contributor to the current opioid crisis. Patients undergoing outpatient general surgery are frequently prescribed opioids after discharge, but the value of this practice remains uncertain. Findings from this pilot trial contribute preliminary data regarding comparative-effectiveness and support the feasibility of conducting a robust full-scale trial to inform evidence-based analgesia prescribing.

2.7 ACKNOWLEDGEMENTS

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2.8 DISCLOSURES

All the authors declare no conflicts of interest in relation to this research.

BRIDGE

Although traditional pilot trials provide important quantitative data (i.e., rates of eligibility, recruitment, retention) to inform the feasibility and design of full-scale RCTs, qualitative methods may contribute relevant information regarding participants' acceptability of the proposed interventions and trial procedures.[82,83] Currently, little is known about patients' and clinicians' views on OFA, willingness to participate in randomized trials, and acceptance of trial methods. Patients' and clinicians' knowledge and attitudes towards novel pain management interventions can contribute to the successful implementation of these interventions in research and clinical settings.[84,85] Chapter 2 reports the findings from a nested qualitative study which explored patients' and clinicians' perspectives and experiences while engaging in a pilot RCT addressing opioid analgesia versus opioid-free analgesia after outpatient general surgery. This study contributed important qualitative evidence to optimize the trial design and better inform evidence-based postoperative analgesia prescribing.

CHAPTER 3

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Opioid-free analgesia after outpatient general surgery: A qualitative study focused on the perspectives of patients and clinicians involved in a pilot trial.

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Running Title

Outpatient general surgery & opioid-free analgesia

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3.1 ABSTRACT

Background

Opioid-free analgesia (OFA) may mitigate opioid-related harms after outpatient general surgery; however, the comparative-effectiveness of this approach should be assessed in robust randomized controlled trials (RCTs). Undertaking an RCT on OFA raises important practical concerns, including surgeon and patient hesitation regarding pain management without opioids. We conducted a qualitative study to explore patients' and clinicians' perspectives and experiences with a pilot trial focused on OFA after outpatient general surgery.

Methods

Patients undergoing outpatient abdominal and breast procedures were randomized to receive post-discharge opioid analgesia (OA) or OFA. Semi-structured interviews with patients and clinicians involved in the trial were conducted to elicit personal perspectives and experiences. Purposive sampling for maximum variation was used to recruit participants with diverse characteristics. Transcribed interviews were assessed using inductive thematic analysis.

Results

Ten patients (5 abdominal, 5 breast) and 10 clinicians (6 surgeons, 2 anesthesiologists, 2 nurses) were interviewed. Five major themes emerged: readiness for trial engagement, pre-trial thoughts about the interventions, postoperative pain experiences, intervention acceptability, and trial refinement. Most patients were open to OFA. Clinicians expressed willingness to prescribe OFA, particularly after less invasive procedures and when using peripheral nerve blocks (PNBs). Concerns were raised regarding the adequacy of pain control and side-effects of non-opioid drugs (e.g., NSAID-induced bleeding, kidney injury). Overall, participants were enthusiastic about the trial and recognized its relevance; clinicians praised the study design and organization, and patients

valued the use of electronic questionnaires. Suggestions for improvements included preventing potential bias arising from the use of PNBs (i.e., via standardization or stratification) and reducing patient burden (i.e., decreasing postoperative questionnaires).

Conclusion

Our findings support that patients and clinicians generally accept the clinical equipoise between OA versus OFA after outpatient general surgery and recognize the need for methodologically robust trials to inform evidence-based analgesia prescribing.

Keywords: opioids, opioid-free analgesia, postoperative pain, general surgery, pain management, qualitative analysis

3.2 INTRODUCTION

Overprescribing opioids to surgical patients is recognized as an important contributor to the current opioid crisis in North America.[86] Surgery often serves as the initial event for opioid-naïve patients to obtain a prescription for opioids and spiral into misuse and addiction.[26,87] Those undergoing outpatient surgery (with planned same-day discharge) are particularly vulnerable as they invariably require some form of analgesia to be taken at home during the first postoperative days. In North America, analgesia for these patients often includes over-the-counter non-opioid drugs [e.g., acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs)] and prescription opioids to be taken 'as needed' in case of breakthrough pain.[24] Under current prescription patterns, approximately 6% of opioid-naïve surgical patients become persistent opioid users postoperatively, i.e., they continue to take the drug for more than three months after surgery.[25,26] Those who do not become persistent users may contribute to the opioid epidemic by diverting unused tablets to others.[28] Of all opioid tablets obtained by surgical patients, 42% to 71% go unused and become a readily available source for diversion.[28] Therefore, evidence-based interventions are urgently required to address opioid-related harms after surgical discharge.

From the perspective of surgeons, the answer to the opioid crisis may be preventing opioid prescribing by using opioid-free analgesia (OFA), which is a common practice in countries outside of North America.[34-37] However, there is a lack of robust randomized controlled trials (RCTs) assessing the comparative-effectiveness of analgesia regimens including opioids (opioid analgesia, OA) versus OFA after postoperative discharge.[46] Given the complexity of well-designed RCTs, pilot studies are critical to assess trial acceptability, feasibility, and to optimize research design.[54] Moreover, undertaking RCTs focused on OFA raises important concerns including surgeon and patient hesitation about pain management without opioids, appropriateness of trial procedures, and

optimal outcome measurement strategy. While traditional pilot RCTs provide important quantitative data (i.e., rates of eligibility, recruitment, retention) to inform the design of larger trials, qualitative methods may contribute relevant information regarding participants' perceptions about trial methodology and interventions.[83] Currently, little is known about patients' and clinicians' views on OFA, willingness to participate in randomized trials, and acceptance of trial methods. Hence, the aim of this qualitative study was to explore patients' and clinicians' perspectives and experiences with a pilot RCT focused on OA versus OFA after outpatient general surgery.

3.3 MATERIALS AND METHODS

This was a qualitative study embedded within a pragmatic, parallel, two-group, assessor-blind, pilot RCT conducted at two university-affiliated hospitals in Montreal, Canada from January to September 2020 (ClinicalTrials.gov ID: NCT04254679). The full description of the pilot RCT methods are available in the Appendix (Study Protocol) and have also been reported elsewhere.[88]

3.3.1 Pilot RCT study design

The pilot study included adult patients (≥18 years) undergoing outpatient abdominal (i.e., cholecystectomies, appendectomies, hernia repairs) or breast surgeries (i.e., lumpectomies, partial and total mastectomies, axillary node dissections). Surgeons' agreement to have their patients in the trial was required for inclusion. Patients were excluded if they had contraindications to any of the drugs used in the trial (i.e., substance use disorder, bleeding disorders, renal or liver impairment), were taking opioids prior to surgery, or had conditions that could interfere with outcome assessment (e.g., cognitive impairment, inability to understand English or French, and limited access to a telephone or computer). Patients who experienced intraoperative or early surgical complications requiring hospital stay were also excluded.

Patients were randomized 1:1 to receive OA (around-the-clock non-opioids and opioid tablets for breakthrough pain) or OFA (around-the-clock non-opioids and increasing doses and/or adding non-opioid drugs for breakthrough pain). Patients' postoperative analgesia regimens are detailed in Table A6 (Appendix). Randomizations were conducted after skin closure by research staff present in the operating room (OR). As OFA was new to our institutions, patients in this group had a 'study hotline' (i.e., a dedicated mobile phone kept with study staff) available 24/7 to report uncontrolled pain. When this line was called, patients were informed about the availability of an opioid prescription at their pharmacy (faxed on the day of discharge). Primary outcomes were *a priori* RCT feasibility criteria, including: >70% screened patients meet eligibility criteria, >50% eligible patients are randomized, and >80% randomized patients complete follow-up. Data regarding patient-reported outcomes (i.e., Brief Pain Inventory, PROMIS-29, and satisfaction with pain management), analgesic intake, unplanned healthcare utilization, and adverse events were obtained up to 4 weeks after surgery. Data was collected by blinded assessors via electronic questionnaires or telephone. Details about the interventions, randomization, blinding, and outcome measurement strategies are available in Appendix (Study Protocol).

3.3.2 Qualitative study design

In this study, we used a qualitative description approach to provide a rich account of patients' and clinicians' perspectives and experiences while engaging in the pilot RCT.[89,90] The study protocol was approved by our institutional research ethics board (ref. MUHC REB 2020-5965) and all participants provided informed consent. Our methods followed O'Cathain's framework for the use of qualitative studies to improve comparative-effectiveness research.[82] Reporting was in accordance with the Consolidated criteria for Reporting Qualitative research (COREQ) (Appendix, Table A9).[91]

3.3.3 Study participants

Patients eligible for the pilot RCT were invited via telephone or email to participate in the qualitative study. To obtain a variety of perspectives, we aimed to recruit patients who consented to participate in the RCT, as well as those who did not consent to participate. Clinicians (surgeons, nurses, anesthesiologists) involved in the perioperative care of trial participants were invited via email. A purposive sampling method with maximum variation was used to improve sample representativeness and ensure diversity in participants' characteristics.[92] *A priori* recruitment quotas for patients focused on diversity in age, gender, surgical procedure, education level, employment status, presence of postoperative complication(s), and consent status (Appendix Table A10). Recruitment quotas for clinicians targeted diversity in years of clinical experience, training background/specialty (general abdominal surgery, breast surgery, anesthesia, nursing), formal research experience (i.e., Masters, PhD), trial site, and number of patients involved in the trial (Appendix Table A11). The targeted sample size was 10 participants (5 patients, 5 clinicians), but interviews continued until thematic saturation was reached (i.e., point after which no new concepts/themes were identified).[93]

3.3.4 Data Collection

Data were collected via individual, semi-structured interviews to allow for a deep understanding of participants' personal views.[94] Three distinct interview guides (available in Appendix) were designed for (1) patients who participated in the trial, (2) patients who declined participation, and (3) clinicians who cared for patients participating in the trial. These guides were collectively drafted, iteratively revised, and pilot tested by our multidisciplinary team to optimize terminology, flow, and prevent redundancy.[95] Interview questions for patients focused on the acceptability of the trial, reasons for consent or non-consent, experiences with the process of recruitment,

interventions and outcome assessment strategy, and areas for improvement in the trial design. Interviews with clinicians focused on acceptability, experiences operationalizing the study, and areas for trial improvement.

Interviews were conducted via telephone, Zoom (https://zoom.us/), or in-person by interviewers familiar with the subject matter and the trial procedures (UD and MP, graduate students), who received dedicated interview training from a senior qualitative researcher (FR, PhD experience in qualitative research). To effectively capture the interview data, interviews were audio recorded, anonymized, and transcribed verbatim by a third-party transcription company (https://vananservices.com/Transcription-Services.php). To ensure accuracy, the interviewers checked all the transcribed interviews against the original audio recordings.

3.3.5 Data Analysis

The transcribed interviews were analyzed using an inductive thematic analysis approach (as described by Braun and Clarke),[96] which provides a flexible analytical approach allowing for themes to be derived from within the data (i.e., the approach is not dependent on a pre-existing theory or framework).[96] Coding was done at the semantic level, staying close to the surface meanings of the data to gather rich descriptions from the viewpoint of the participants.[97] The analysis was conducted independently by two researchers (UD and MP) with disagreements resolved by consensus arbitrated by a senior researcher (JF or TN, both with PhD experience in qualitative research). A reflexive approach was also used, acknowledging that the researchers views and past experiences can be reflected in the data analysis and interpretation.[98]

The software MAXQDA 2020 (VERBI Software, 2019) was used to facilitate the thematic analysis process, which followed six-steps:[96] (1) coders familiarized themselves with the interview transcripts, (2) coders generated initial codes and met for peer-debriefing (to establish

trustworthiness and internal validity),[99] (3) codes were clustered into preliminary candidate themes, (4) themes were reviewed and tested for referential adequacy by a senior researcher (TN), (5) a thematic map was generated with input from all team members and revised iteratively until reaching a final codebook (Appendix Table A12), and (6) themes for which saturation was reached were reported as meaningful perspectives about the pilot RCT interventions and procedures. Saturation was assessed iteratively using a saturation grid,[100] and considered to have been reached when no new themes emerged from two consecutive interviews (Appendix Figure A12).

3.4 RESULTS

Recruitment of participants occurred between January and September 2020. All the surgeons who conducted eligible surgeries during the study period (n=15) agreed to have their patients recruited. In total, 224 patients were assessed for eligibility, 163 met inclusion criteria (73%), and 93 consented for randomization (57%). A total of 76 patients (39 OA and 37 OFA) were included in the intention-to-treat analysis. All the RCT feasibility criteria were fulfilled. Overall, Brief Pain Inventory (pain intensity and interference), PROMIS-29, and satisfaction data were comparable between groups. Twenty-two patients (56%) randomized to OA did not take opioids. One patient (3%) randomized to OFA received an opioid prescription. Unplanned healthcare utilization was required by 6 patients in the OA group (15%) and 1 patient in the OFA group (3%). Common adverse events were constipation (41% vs. 32%) and nausea (OA 21% vs. OFA 16%).[88,101]

Qualitative interviews were conducted between May and December 2020. All recruitment quotas were met, resulting in a diverse sample of patients and clinicians. Twelve patients were invited to take part in the interviews, two refused (not interested) and 10 consented (characteristics detailed in Table 3-1). Among the patients interviewed, 8 participated in the pilot RCT and 2 did not consent to participate. Eleven perioperative care clinicians were invited to take part in the

interviews; one refused (lack of time) and 10 consented (characteristics detailed in Table 3-2). Interviews with patients lasted between 12 and 50 minutes; interviews with clinicians lasted between 15 to 35 minutes. Thematic saturation was reached at 20 interviews (Appendix Figure A12).

Table 3-1. Patients' baseline and demographic characteristics.

Characteristic	*n* (%)
Total No.	10
Age, mean (SD), years	54 (23)
Age, years	
≤ 30 years	2 (20)
≥ 65 years	4 (40)
Female	6 (60)
Male	4 (40)
Surgery	
Abdominal[a]	5 (50)
Breast[b]	5 (50)
Education level	
≤ High school	2 (20)
≥ University degree	8 (20)
Official employment status	
Working/studying	6 (60)
Unemployed	1 (10)
Retired	3 (30)
Postoperative complications after discharge	1 (10)
Participated in the Pilot RCT	
Yes	8 (80)
No	2 (20)

Data are n (%) unless otherwise stated.
[a] Laparoscopic cholecystectomy (n=2), open inguinal hernia repair (n=2), laparoscopic inguinal hernia repair (n=1)
[b] Partial mastectomy (n=2), partial mastectomy with sentinel lymph node biopsy (n=2), total mastectomy with reconstruction (n=1)

Table 3-2. Clinicians' demographic characteristics

Characteristic	*n* (%)
Total No.	10
Female	7 (70)
Male	3 (30)
Years of clinical experience (after residency)	
≤ 5 years	2 (20)
≥ 15 years	8 (80)
Practice location	
Montreal General Hospital	6 (60)
Royal Victoria Hospital	4 (40)
Training background/specialty	
Surgery	6 (60)
Abdominal	4 (40)
Breast	2 (20)
Anesthesia	2 (20)
Nursing	2 (20)
Received formal research training (MSc, PhD)	5 (50)
Number of patients involved in trial[a]	
≥ 3 patients	4 (67)
< 3 patients	2 (33)

Data are n (%) unless otherwise stated.
[a] Surgeons only.

Thematic analysis of the interviews revealed five overarching themes related to perspectives and experiences with the pilot RCT: (1) readiness for trial engagement, (2) pre-trial thoughts about the interventions, (3) postoperative pain experiences, (4) trial and intervention acceptability, and (5) trial refinements for the full-scale RCT (Figure 3-1 and Table 3-3).

Table 3-3. Themes and representative quotes

Themes	Sub-themes	Representative quotes
Readiness for trial engagement	Drivers to participation	It helps people not to rely on, I mean there's lots of things they can do these days to cope with pain. You don't necessarily need heavy medication, I find. But look, if you're doing the study, hopefully you don't have to prescribe so much medication because they're not needed… Every time I [undergo surgery], they give me tons of medication and I end up returning them. I mean, if this study is going to help reduce the amount of medication being used by patient, not unnecessarily, then it will be very good. (Consenting patient #7, received OA)
	Drivers to non-participation	If I was in a control group and not getting opioid pain killers, I knew from previous experience, I was going to be affected. I didn't want to risk potentially the chance that I needed extra time to go through the process of finding something else that worked. (Non-consenting patient #1)
Pre-trial thoughts about the interventions	Thoughts favoring opioid-free analgesia	Yeah, I did have the preference of not being in the opioid group because I felt like out of sight, out of mind. If I didn't have to deal with it, there wouldn't be a risk. As I said, the opioid crisis, that was the only type of concern that was in my head. (Consenting patient #3, received OA)
	Thoughts favoring opioid analgesia	I was always biased to think that you didn't always need opioids but, once in a while, you do so the patients who need it should have access to it. But you don't know who they are until the next day. (Surgeon #5)
Postoperative pain experiences	Experienced minimal pain	It was more of a, if anything, like an ache or a bruise if you touched it sort of thing, but not a severe pain at all. (Consenting patient #1, received OFA)
	Experienced considerable pain	I work out probably four, five times a week, so I wasn't able to do any workouts. I had to be very careful moving around. It was more of a precautionary posture than pain in my day-to-day life. Within a week, I was walking around pretty good, but within two weeks, I couldn't feel [the pain]. I just had to be careful not to lift anything. (Non-consenting patient #2)
Trial and intervention acceptability	Positive experience with participation	It made me really think about the medication I'm using a little bit, but I already do think about medication because I keep a schedule of what I take in terms of meds. I also want to be careful about how much of what I take each medication. How could affect me in my life. (Consenting patient #6, received OA)
	Coherent interventions	But I do think that there is a certain comfort in saying… from the point of view of the doctor, to know that [the backup opioid prescription] is there and it's prescribed so that if pain is severe [patients] have access to that without significant administrative work from the doctor's side. (Surgeon #4)
	Appropriate data collection process	They were very thorough. Not only did it ask me about my physical pain, but it also asked about my mental capacity of how I was feeling and that kind of stuff, so I appreciated all the questions. (Consenting patient #2, received OA)
	Sound research methods	I think the timing of the randomization was appropriate and wasn't disruptive in the OR. (Surgeon #6)
Trial refinement for full-scale RCT	Optimizing patient screening and randomization	[T]here was an instance where the patient had the chronic kidney dysfunction, and the patient was randomized… So, I think that doubly screening out these high-risk patients would be something to improve in future trials. (Anesthesiologist #1)
	Optimizing outcome assessment	At that point, the interest is how functional the patient remains despite the pain that the patient feels. Functional status is very important, and probably psychological assessment as well. (Anesthesiologist #2)
	Optimizing other pain management strategies	But I think it has to also be with a very good understanding that patients shouldn't expect that they will be completely pain-free. I think that's also a misunderstanding on the part of the patient, that they should expect some degree of pain and they shouldn't expect to have zero pain post-surgery. So,

		I think once that is clear, that will also kind of reduce the need for using opioids. (Surgeon #6)
	Addressing potential sources of bias	I think there's some variability in technical techniques [such as] an anesthesiologist's comfort in doing certain types of peripheral nerve blocks. (Anesthesiologist #1)
	Decreasing participant burden	I thought it was going be a short study and I was willing to participate in short studies. It turns out to be a long study. I'm disappointed that it took so long to complete. (Consenting patient #6, received OA)
	Ameliorating communication strategy	I think as we move forward, I think we have to sit down with anesthesia and come up with a global plan. We can't just do nerve blocks in some patients and not in others. We need to have a coherent non-opioid approach which involves anesthesia. (Surgeon #1)

OA = opioid analgesia; OFA = opioid-free analgesia

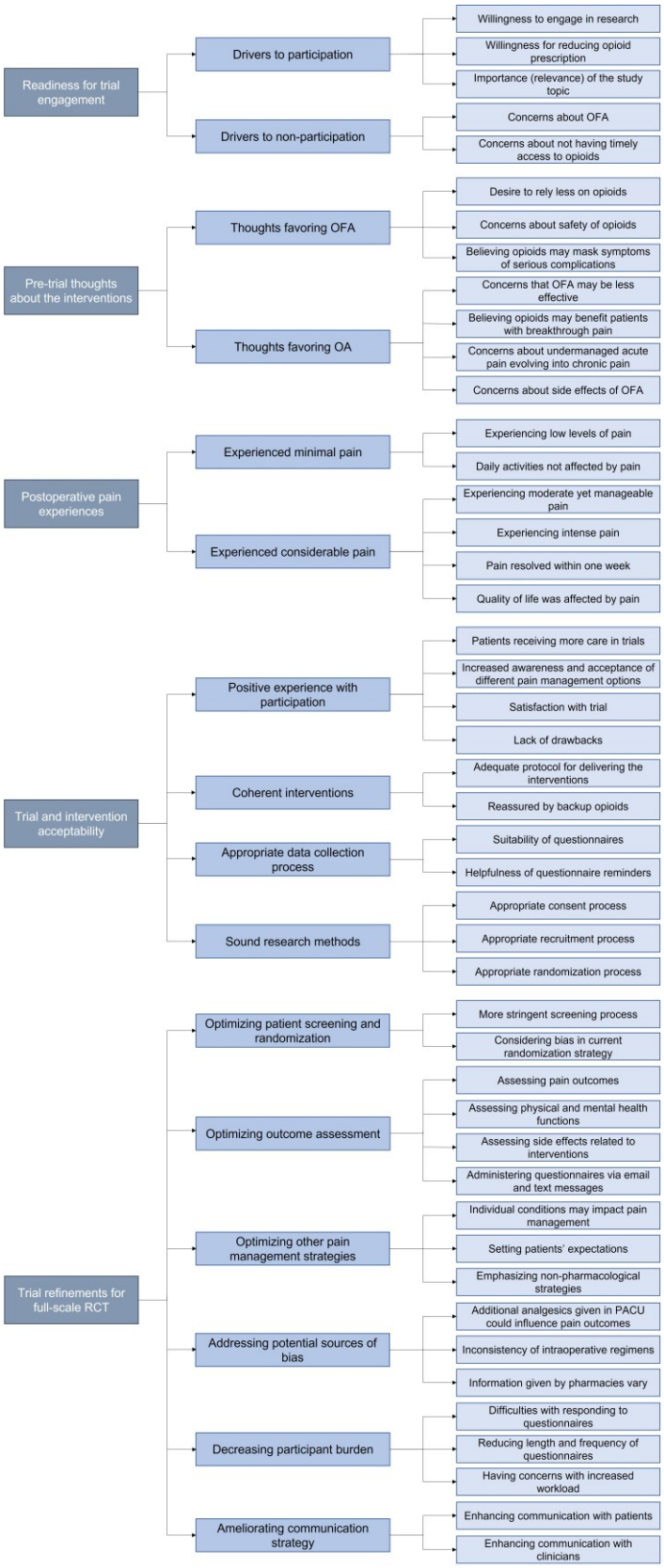

Figure 3-1. Thematic map

3.4.1 Readiness for trial engagement

Drivers to participation

Drivers that motivated patients and clinicians to engage in the pilot RCT included willingness to contribute to evidence-based practice, research progress, and helping patients who will undergo surgery in the future. Interviewees generally recognized the importance of the research topic given the current opioid crisis and supported the need to reduce postoperative opioid overprescribing (Figure 3-1 and Table 3-3).

Drivers to non-participation

Patients who declined to be randomized revealed concerns about ineffective pain control using OFA and mentioned previous experiences of effective pain relief from using opioids. These patients were also concerned about not having timely access to opioids in case of breakthrough pain and risking pain while searching for effective treatments (Figure 3-1 and Table 3-3).

3.4.2 Pre-trial thoughts about the interventions

Thoughts favoring opioid-free analgesia

Many patients indicated preferences for relying less on medications (particularly opioids) for postoperative pain management. These patients expressed 'dislike' of opioids and had negative feelings about receiving an opioid prescription. Clinicians' preferences for OFA were shaped by their support of multimodal analgesic approaches and educating patients to avoid using opioids given the risk of addiction and other side effects (e.g., constipation, nausea). Additionally, some clinicians suggested that using opioids may prevent patients from promptly seeking care when severe or ongoing pain indicates serious postoperative complications (Figure 3-1 and Table 3-3).

Thoughts favoring opioid analgesia

Some patients and clinicians expressed skepticism regarding the effectiveness of OFA and stated that opioids may benefit a subset of patients who experience breakthrough pain. Clinicians, specifically, expressed concerns about inadequate pain control among patients undergoing more extensive procedures (e.g., open abdominal procedures, mastectomy with lymph node dissection). Some were also worried about the side effects of non-opioid analgesics (e.g., NSAIDs increasing the risk of bleeding and renal complications) and the risk of poorly managed acute pain progressing to chronic postoperative pain (Figure 3-1 and Table 3-3).

3.4.3 Postoperative pain experiences

Experienced minimal pain

Many patients reported experiencing low levels of postoperative pain by, for example, stating that their pain was more like a 'bruise or an ache' (Figure 3-1 and Table 3-3). For these patients, pain was manageable using OFA and they were able to resume activities within a few days (i.e., being able to sleep, perform simple chores, and manage daily tasks without help).

Experienced considerable pain

Some patients experienced considerable pain in the first postoperative days which affected their ability to resume daily activities (i.e., sleep, physical chores, and ability to partake in household responsibilities). Most of these patients described that their pain subsided within one week and many felt no need to take additional pain medications (Figure 3-1 and Table 3-3).

3.4.4 Trial and intervention acceptability

Positive experience with participation

Patients and clinicians were generally enthusiastic about the trial and recognized its relevance. Clinicians appreciated that patients may benefit from additional medical care and frequent check-ups while participating in the trial. Likewise, patients felt cared for with the questionnaire follow-ups, reporting increased awareness of the recovery process and postoperative pain management options. Overall, participants indicated minimal drawbacks from trial participation and reported no concerns about the trial conduct (Figure 3-1 and Table 3-3).

Coherent interventions

Patients and clinicians found the trial interventions and design to be acceptable, coherent, and satisfactory. Most surgeons stated that having the backup opioid prescription was reassuring, and they appreciated the availability of opioids if pain was not well-controlled by patients with OFA (Figure 3-1 and Table 3-3).

Appropriate data collection process

Experiences with the data collection process were positive and patients valued the option to respond to outcome questionnaires electronically. Many patients preferred to receive the questionnaires by email to complete at their leisure and found the frequency and length of follow-ups to be appropriate. Patients perceived the follow-up questions relating to pain and physical and mental health to be thorough, clear, and relevant to their recovery. Additionally, patients appreciated the reminders to complete the questionnaires and found them to be helpful (Figure 3-1 and Table 3-3).

Sound research methods

Patients and clinicians found the recruitment and consent process to be transparent and informative. Most participants indicated that it was not necessary to change the way patients are approached for study participation in the full-scale trial. Surgeons found the randomization strategy to be appropriate and were comfortable with signing discharge prescriptions in the OR (Figure 3-1 and Table 3-3).

3.4.5 Trial refinements for the full-scale RCT

Optimizing patient screening and randomization

Two patients were excluded from the pilot trial after randomization because they had contraindications to NSAIDs not documented in their electronic medical records. To prevent future post-randomization exclusions, some clinicians suggested that screening could be optimized by confirming patient's eligibility with surgeons and anesthesiologists in the OR prior to randomization. Some clinicians also suggested that patients should be randomized prior to PACU discharge (rather than in the OR) to optimize concealment of allocation (Figure 3-1 and Table 3-3).

Optimizing outcome assessment

To optimize outcome measurement, clinicians emphasized the importance of assessing the impact of the intervention on pain intensity and on physical and psychological functions. Also, many clinicians were concerned with the intervention's side-effects, particularly NSAIDs, suggesting that side-effects such as bleeding and acute kidney injury should be thoroughly addressed in future RCTs (Figure 3-1 and Table 3-3).

Optimizing other pain management strategies

Suggestions given to improve the trial included considering surgical characteristics that may impact pain after postoperative discharge [i.e., using peripheral nerve blocks (PNBs) for more extensive surgeries]. Clinicians also emphasized the importance of setting patient's pain expectations preoperatively (i.e., some pain is expected after surgery). Furthermore, some patients expressed a desire to learn more about non-pharmacological strategies to cope with pain (Figure 3-1 and Table 3-3).

Addressing potential sources of bias

Feedback from clinicians included addressing potential sources of bias that may influence patient pain outcomes after discharge. Some clinicians expressed concerns about the non-standardized use of PNBs, suggesting that intraoperative analgesia techniques should be standardized in the future RCT (by e.g., stratified randomization). Others mentioned that randomizing patients in the OR may lead to performance bias in the post-anesthesia care unit (PACU) where patients in the OFA group could receive additional analgesia (Figure 3-1 and Table 3-3).

Decreasing participant burden

Feedback regarding trial processes included reducing patient burden by decreasing the length of follow-up and frequency of postoperative questionnaires (Figure 3-1 and Table 3-3).

Ameliorating communication strategy

Patients expressed that communication with researchers during the trial could be further improved by providing clear instructions (in verbal and written formats) on how to take different types of pain medications. Also, clinicians highlighted that continual collaboration with anesthesiologists in the planning of future trials would be necessary to devise a plan to address the inconsistency in

intraoperative interventions (i.e., the use of PNBs). Lastly, nurses emphasized the importance of widely disseminating trial's information to PACU and OR staff to ensure research procedures are coherent and smooth (Figure 3-1 and Table 3-3).

3.5 DISCUSSION

Patients undergoing outpatient general surgery are frequently prescribed opioids to be taken after hospital discharge, but the value of this practice remains uncertain. Findings from this qualitative study suggest that patients and clinicians generally accept the clinical equipoise between OA versus OFA after outpatient general surgery and recognize the need for methodologically robust trials to inform evidence-based analgesia prescribing.

Patients were generally motivated to take part in the trial. Our findings indicate that their participation was driven by altruism (desiring to contribute to research and improve care for others) and personal interests (desire for close follow-up, interest in the research question). Previous literature supports that patients are initially inclined to participate in a trial to help others (social benefits) and that their final decision to participate is solidified by recognizing personal benefits.[102,103] Likewise, patients perceived no drawbacks (no significant disadvantage or burden) from taking part in the trial during the perioperative period. Prior to trial participation, some patients held strong opinions that favored either OA or OFA. They were generally aware of the risks of opioid medications (i.e., misuse, addiction, other side effects) and expressed a desire to reduce postoperative opioid prescribing. However, some patients expressed concerns about the effectiveness of OFA, which is in line with previous literature reporting that patients often believe opioids are the most powerful medication to treat postoperative pain,[104] despite the lack of clear evidence.[38,43-45,49] To optimize future trials, the findings highlighted above indicate the importance

of tailoring recruitment strategies to address patients' concerns and emphasize the clinical equipoise between OA and OFA, in addition to providing clear information about trial procedures and expected time commitment.[105-107]

Most patients found the outcome measurement strategy to be appropriate and acknowledged the utility of capturing pain outcomes daily during the first seven days after surgery. Few patients found responding to daily postoperative questionnaires to be challenging while recovering from surgery, while others felt that a 1-month follow-up was too long. To decrease participant burden, one patient suggested that the duration of postoperative follow-up should only focus on the first postoperative days, when pain is usually present. In previous literature, patients tended to find studies extending beyond 1 month after surgery to be more burdensome.[108] In future trials, outcome assessment strategies should aim to optimize the length of questionnaires and limit the follow-up period.[109] Overall, patients appreciated being able to receive the survey via both email and text and valued the electronic data collection method.

All of the surgeons who conducted eligible procedures during the study period agreed to have their patients recruited, which attests to their support of the proposed research. However, concerns were raised regarding the risk of inadequate pain control when patients are offered analgesia without opioids, which may potentially lead to increased emergency department visits and patient dissatisfaction.[31,81] The quantitative findings from our pilot trial supported that pain outcomes and patient satisfaction were comparable between the study groups and only one patient (3%) randomized to OFA received an opioid prescription due to 'uncontrolled' pain.[88,101] These findings contribute evidence regarding the feasibility of OFA and support the need for a full scale, definitive trial. Some clinicians were also concerned about the safety profile of non-opioid drugs, especially the risk of postoperative bleeding and kidney injury induced by NSAIDs. There is still great debate

about the safety of prescribing NSAIDs postoperatively;[110,111] however, a recent meta-analysis supported that NSAIDs are unlikely to be the cause of bleeding complications,[112] while their impact on risk of acute kidney injury remains inconclusive.[113] Given the rates of adverse events attributable to NSAIDs are relatively low after outpatient general surgery, evidence in this field requires the conduct of robust RCTs with larger sample sizes or meta-analyses of high-quality RCTs. Clinicians also raised concerns about the risk of poorly managed acute pain progressing to chronic postoperative pain.[114] While risk of chronic pain was not one of the endpoints assessed in our pilot trial, this outcome should be addressed in future full-scale RCTs focused on OA versus OFA.

Interview data revealed clinicians were enthusiastic about the trial, recognized its relevance, and praised the study design and organization. In the interviews, clinicians found that patient randomization in the OR was acceptable and had minimal impact on their routine practice. However, some suggested that randomization prior to PACU discharge may ensure concealment of allocation and prevent performance bias.[115] Despite these benefits, the latter strategy may be impractical to some surgeons who often write their prescriptions in the OR after skin closure. Clinicians also raised concerns about the inconsistent use of PNBs, suggesting that intraoperative analgesia techniques should be standardized or accounted for in future RCTs (e.g., by stratifying randomization). Another relevant feedback from clinicians is that the trial should be more widely disseminated to perioperative care staff via different modalities (e.g., posters, emails, written materials) to ensure coherence and smooth trial coordination.

The use of a robust qualitative research approach is a major strength of this study. We used a maximal variation sampling method to include a diverse sample of patients and clinicians and thus account for potential differences in perspectives, including experiences with the feasibility of

implementing OFA in outpatient surgery settings. We also collected insights from patients who declined to take part in the trial, which furthered our understanding regarding barriers to recruitment. An inductive thematic analysis was conducted, which allowed us to derive meaningful themes that were strongly linked to the data.[96] Interview transcripts were coded in duplicate, reviewed by qualitative research experts, and assessed for thematic saturation to increase the trustworthiness of results. The commonality of views and experiences expressed by participants attests to the robustness of our findings.

This study is subject to some limitations. As we targeted common views amongst different stakeholders involved in the trial, comparison between different subgroups (e.g., patients vs. clinicians, nurses vs. physicians, patients receiving OA vs. OFA) was beyond our scope. We did not target within-group thematic saturation, which prevents meaningful comparisons. Additionally, our pilot trial did not include patients who could not communicate in English or French, which limited the participation of patients from ethnically diverse backgrounds who may hold different perceptions about postoperative pain management. As a qualitative study, the rigor of our findings should be judged by their plausibility rather than generalizability, and sample size targeted thematic saturation rather than 'statistical power'.[116] Lastly, our participant sample was drawn from a single academic centre in Canada; therefore, our results may not represent the views of patients and clinicians from other practice settings.

3.6 CONCLUSION

In summary, findings from this qualitative study suggest that patients and clinicians support the importance and feasibility of conducting randomized trials focused on the comparative-effectiveness of OA versus OFA after outpatient general surgery. Lessons learned from this study

should be used to optimize trial design to better inform evidence-based postoperative analgesia prescribing.

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3.8 DISCLOSURES

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CHAPTER 4

CONCLUSION & FUTURE DIRECTION

The overprescription of opioids to surgical patients is recognized as a notable contributor to the North American opioid crisis.[9,10] Patients undergoing outpatient general surgery are frequently prescribed opioids after discharge, but the value of this practice remains uncertain.[50] Currently, there is a lack of high-quality comparative-effectiveness studies to determine the value of prescribing opioids at discharge following outpatient general surgery.[50] The research reported in this thesis laid the groundwork for future trials aimed to address this research gap. By addressing the overprescription element of the opioid crisis, our research program tackles the first pillar of the New Canadian Drugs and Substances Strategy (CDSS), i.e., preventing problematic drug and substance use supported by a strong evidence base.[117] Alternatives to opioids are often overlooked by North American surgeons while, whenever possible, they should be incorporated as the foundation of postoperative analgesia to prevent postoperative opioid-related harms.

The first study in this thesis, a pilot RCT, assessed the feasibility of conducting a full-scale RCT aimed at comparing opioid analgesia (OA) vs. opioid-free analgesia (OFA) after hospital discharge following outpatient general surgery. The trial was welcomed by all the stakeholders involved (i.e., funders, ethics committee, patients, scientists, surgeons, anesthesiologists, and other perioperative care clinicians) and all *a priori* feasibility criteria (i.e., rates of eligibility, consent, randomization, lost to follow-up) were fulfilled. Finally, postoperative pain outcomes (pain intensity and interference) were comparable between the interventions. Findings from this study support the feasibility of conducting a full-scale RCT and contribute preliminary data regarding the comparative-effectiveness and safety of OFA after postoperative hospital discharge.

The second study in this thesis used a qualitative description approach to provide important qualitative insights which advanced our understanding of patients' and prescribers' attitudes towards OFA and their experiences with the pilot trial procedures (i.e., recruitment, randomization, and data collection strategies). Our findings supported that patients and clinicians generally accept the clinical equipoise between OA versus OFA after outpatient general surgery and recognize the need for methodologically robust trials to inform evidence-based analgesia prescribing. Overall, participants were enthusiastic about the trial and recognized its relevance, clinicians praised the study design and organization, and patients valued the use of electronic questionnaires.

Valuable venues to optimize future full-scale trials on OFA emerged from this thesis. These include reducing participation burden, preventing bias arising from regional analgesia techniques, and improving communication with trial stakeholders. To reduce participant burden, it was suggested that the daily follow-up questionnaires be administered only for the first 5 postoperative days (instead of 7 days); participants in the pilot trial reported that this duration would be sufficient enough to capture the period of acute postoperative pain. Additionally, although peripheral nerve blocks (PNBs) for regional analgesia are widely used after outpatient abdominal and breast procedures, their implementation is not standardized and often dependent on surgeons' and anesthesiologists' preferences. One way to address potential biases that may arise from the inconsistent use of PNBs would be to include an additional stratum within the randomization strategy to ensure balance in the distribution of different analgesia approaches across treatment groups. Lastly, to ensure coherence and smooth trial coordination for a full-scale trial, efforts to widely disseminate trial information to patients and perioperative care staff via different modalities should be undertaken. These methods may include providing written explanations to patients on how to take discharge medications, arranging channels of communication for patients to reach out

to researchers and clinical staff during the trial, distributing trial information posters in waiting areas and clinician lounges, and circulating emails about trial updates to perioperative care staff.

Moving forward, the findings and lessons learned from this thesis' research are currently being used to inform the proposal for a full-scale, definitive RCT focused on the comparative-effectiveness of OA versus OFA after outpatient general surgery. Funding for the full-scale trial will be sought from major governmental research agencies [Canadian Institutes of Health Research (CIHR), US National Institutes of Health (NIH), and US Department of Defense (DoD)]. The proposed full-scale RCT has the potential to contribute practice-changing evidence to inform guidelines and support sustainable advances in analgesia prescribing practices after outpatient general surgery. By laying the groundwork for future high-quality trials, the research reported in this thesis provides an essential first step for building a strong body of evidence to mitigate the negative downstream effects of postoperative opioid overprescribing in North America.

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APPENDIX

STUDY PROTOCOL AS APPROVED BY ETHICS

Project title: Opioid-free analgesia after outpatient general surgery: A pilot randomized controlled trial

Rationale

Canada is in the midst of an epidemic of opioid use and abuse fueled by increased prescriptions by physicians. Overprescription has been implicated as a driving force behind the growing number of overdoses and deaths caused by opioids. Canada has the second highest rate of opioid prescription per-capita in the world after the United States.[1] Physicians wrote on average one opioid prescription for every two Canadians in 2017.[2] In the same year, at least 4100 opioid-related deaths occurred across Canada.[3] This death toll increased to 4460 in 2018, which represents an average of 12 Canadians dying from opioid overdoses every day.[3] The estimated economic cost of opioid misuse in Canada, accounting for health, justice, lost productivity and other direct costs, tops $3.5 billion per year.[4] As a response to this grim statistic, the federal Minister of Health has made combatting the 'opioid crisis' a top priority.[5]

Surgery often serves as the initial event for opioid-naïve patients to obtain a prescription for opioids and spiral into misuse and addiction.[6,7] Those undergoing outpatient surgery (i.e., with same day discharge), which represent nearly 80% of all surgeries performed in Canada and the United States,[8] are particularly vulnerable as they invariably require some form of analgesia to be taken at home during the first postoperative days. In North America, analgesia for these patients often includes over-the-counter non-opioid drugs [e.g., acetaminophen and/or non-steroid anti-inflammatory drugs (NSAIDs)/Cox-2 inhibitors (COX-2)] and prescription opioid tablets to be taken 'as needed' in case of breakthrough pain. With this current prescription pattern, up to 1-in-10 patients become persistent opioid users postoperatively, i.e., they continue to take the drug for more than three months after surgery.[6,9,10] Those who do not become persistent users may also contribute to the opioid epidemic by diverting unused tablets for nonmedical use by others. A recent systematic review suggests that of all opioid tablets obtained by surgical patients 42% to 71% go unused.[11] In other words, they are prescribed unnecessarily and become a readily available source for diversion. It is estimated that over 50% of people who abuse opioids obtain the drug via diversion from friends or relatives with unused prescriptions.[12] Although the prescription of opioids after outpatient surgery seems harmless to many, postoperative overprescription is an urgent element of the opioid crisis given how commonly it may contribute to misuse, diversion, addiction and death.

From the perspective of surgeons and other perioperative care clinicians, the answer to the opioid crisis may be preventing opioid prescriptions whenever possible using opioid-free analgesia. In European countries, postoperative discharge prescriptions commonly include only non-opioid drugs while, interestingly, pain-related outcomes (i.e. satisfaction with pain treatment) are often superior to North America.[13-15] Moreover, evidence regarding the benefits of postoperative opioids has largely relied on unimodal, single-dose studies conducted for regulatory purposes under strict experimental conditions.[16] Arguably, a more appropriate approach to guide clinical practice is to examine the impact of postoperative opioids in 'real-world' conditions, where analgesia strategies are often multimodal and pain treatment span several days. Data from a scoping review recently completed by our research group (currently under peer-review for publication) supports that the number of comparative studies in this field is limited, while existing small trials often challenge the value of adding opioids to multimodal analgesia regimens.[17-19] Lack of evidence in this field

means that the decision to prescribe opioids after outpatient surgery largely depends on healthcare culture and surgeon preference. Hence, there is an urgent need for robust randomized clinical trials (RCTs) to guide clinical decision-making.

Due to the complexity inherent to well-designed RCTs, pilot studies are critical to assess acceptability, test logistical aspects, optimize design and build the capacities required for a full-scale trial.[20] Undertaking an RCT of opioid-free analgesia raises important practical concerns including: surgeon and patient hesitation about pain treatment without opioids, decision regarding participation under preoperative stress, treatment adherence and optimal measurement strategies. Thus, the overarching objective of the proposed pilot study is to investigate the feasibility of conducting a full-scale, pragmatic RCT aimed to estimate the extent to which analgesia regimens including opioids (opioid analgesia, OA) impact postoperative outcomes after outpatient general surgery in comparison to regimens that are opioid-free (opioid-free analgesia, OFA). By addressing the prevention of opioid prescription after outpatient surgery, this proposal tackles the first pillar of the New Canadian Drugs and Substances Strategy (CDSS), i.e., preventing problematic drug and substance use supported by a strong evidence base.[21]

Specific research objectives

PART 1. Main study (Pilot RCT)

1.1. To estimate the proportion of screened patients who meet eligibility criteria.

1.2. To assess the willingness of surgeons to recruit/randomize patients undergoing different surgical procedures.

1.3. To estimate the proportion of eligible patients who consent to randomization.

1.4. To estimate the proportion of patients who adhere to the interventions proposed.

1.5. To estimate follow-up completion rates.

1.6. To inform the calculation of sample size requirements for a full-scale RCT.

PART 2. Embedded qualitative study

2.1. To inform, via qualitative research methods, optimal study design of a full-scale RCT by assessing patient and clinician perspectives on trial conduct, participation, interventions and measurement strategy.

Methods

PART 1. Main study (Pilot RCT)

This study will be a parallel, two-group, assessor-blind, pilot randomized trial with participants individually allocated on a 1:1 ratio to treatment with either OA or OFA. To maximize applicability of the study to current perioperative care settings, the trial was designed to be pragmatic; i.e. it will be undertaken in routine clinical practice under "real world" conditions. Eligibility criteria will facilitate enrollment of diverse patients undergoing outpatient surgery (day surgery) and interventions will be delivered with flexibility in medication selection. An embedded qualitative study will be conducted to help optimize trial design based on clinicians' and patients' perspective.[22] The study protocol will be reviewed by the McGill University Health Centre (MUHC) Research Ethics Board and patient recruitment will start after ethics approval. All participants will sign a written consent form and a paper copy of the form will be attached to the patient medical chart. Trial registration and protocol information will be made available at the

ClinicalTrials.gov website. The planned flow of participants through the study is summarized in Figure A3. A trial management team (TMT), composed by trial leaders (Drs. Fiore, Baldini and Feldman) and trial managers (Ms Pepa Kaneva, Ms Uyen Do and Mr Charbel El Kefraoui) will meet weekly to discuss the progress of the trial and address any issues that may arise.

Patients

Adult patients (over 18 years old) undergoing elective outpatient surgery (with planned discharge same day on the day of the operation) in two sites of the McGill University Health Centre (MUHC) in Montreal, Canada (Montreal General Hospital and Royal Victoria Hospital) will be considered for inclusion. Eligibility will span a wide range of general surgery procedures that are routinely conducted with same day discharge, including procedures in abdominal (i.e., cholecystectomies, hernia repairs) and breast surgery (i.e., lumpectomies, partial and complete mastectomies, axillary node dissections).

As a pragmatic trial, we will keep exclusion criteria to the minimum necessary to ensure both patient safety and internal validity. Patients with intraoperative or early postoperative complications (i.e., diagnosed in the Post-Anesthesia Care Unit (PACU)) that require postoperative hospital stay will be excluded. Other reasons for exclusion are: contraindications to any of the drugs used in the trial according to Health Canada Monographs (i.e. active substance use disorder, pregnancy, severe heart failure, allergy, active symptomatic peptic ulcer or gastrointestinal bleeding, bleeding disorders, severe renal or liver impairment),[23-25] conditions that could interfere with outcome assessment [e.g., cognitive impairment, inability to speak English or French, difficulty to be reached after surgery (e.g., limited access to a telephone or a computer)].

Overview of recruitment and consent procedures

(1) Eligible patients scheduled for elective outpatient general surgery will be informed about the study by their primary surgeon during the preoperative surgical consultation, (2) those who are interested in the study will be advised by the treating clinician that a member of the study group will contact them to discuss the study in detail during their subsequent standard visit to the preoperative assessment clinic or by telephone (if the clinic is bypassed), (3) patients who are eligible and interested in participating will be asked to sign the consent form and complete the study's preoperative questionnaires in the preoperative clinic or at home. In the latter case, consent will be obtained via pre-paid mail and preoperative questionnaires will be completed online or by phone. It will be up to patients to choose the preferred method of completing the questionnaires.

Trial posters will be displayed in waiting areas of the MGH and RVH preoperative clinics to raise awareness of the study for both patients and clinicians. Study promotional materials are attached to this application (Figures A1-10 and A1-11).

Randomization and blinding

Treatment allocations will be concealed until patients are deemed ready to be discharged home from the PACU – i.e., when a discharge order is signed by the primary surgeon, or a delegated clinician member of his/her team. Randomization will be conducted via a secure web-based randomization service (www.sealedenvelope.com). Research staff will have password-protected access to the randomization website by means of a computer or smart phone. No personal information about participants will be entered in this platform. To yield balanced yet unpredictable groups, randomization will use computer-generated, permuted, balanced blocks of randomly varying size (2, 4 or 6). To achieve group balance for important covariates, randomization will be stratified by procedure type (abdominal, breast). Participants and clinicians will be informed

verbally of the treatment allocation at the point of randomization. The primary surgeon, or a delegated clinician member of his/her team, will be responsible for signing a pre-written analgesia discharge prescription in accordance to the treatment that patients have been allocated to.

Participants and treating clinicians (i.e. surgeons, anesthetists, and nurses) will not be blinded to treatment allocation due to the complexity of the medication prescribing strategies. To reduce potential risk of detection bias (systematic differences between groups in how outcomes are determined), outcome assessors will be blinded to treatment allocation. Patient-reported outcomes and treatment adherence data will be collected via self-administered electronic questionnaires distributed using REDCap (http://project-redcap.org/) and completed by patients via smartphone, tablet or personal computer. Electronic outcome data will be transmitted directly to the REDCap database and verified by a blinded assessor. Adherence data will be verified by unblinded study staff. Patients who are not computer savvy, have limited access, or prefer non-electronic assessment will complete the questionnaires via telephone interviews with a blinded assessor; in this case, data will be recorded in paper forms and subsequently transferred to the REDCap database. Prior to every telephone interview, patients will be reminded not to disclose their allocation status or information about pain medications. To prevent unblinding, telephone follow-ups to monitor treatment adherence will be done by a team member not involved in outcome assessment.

Outcome data that are not patient-reported (e.g., postoperative complications, unplanned healthcare utilization, chronic opioid use) will be obtained from medical records by a blinded assessor. Any inadvertent unblinding will be reported. Effectiveness of blinding will be estimated by asking assessors to guess patients' group allocation at one month after surgery (after the last patient questionnaire is responded). Statistical analysis will also be blinded with information regarding allocation protected by codes that will be revealed only after all analyses are completed.

Interventions

Opioid analgesia (OA) group

Patients randomized to the OA group will receive the current standard of care in the participating centers, which includes the prescription of around-the-clock non-opioid analgesics (acetaminophen and/or NSAIDs/COX-2) and a supply of opioids to be used as a rescue in case of breakthrough pain (i.e., pain that erupts while a patient is already medicated with painkillers). Prior to hospital discharge, patients will undergo a medication education session with the PACU nurse and be advised to fill their prescription at a pharmacy of their preference. Medication education sessions with a nurse prior to discharge are part of standard care at MUHC. In light of the pragmatic nature of this trial, the specific round-the-clock analgesia and rescue opioid regimens will be determined by the patient's primary surgeon considering the surgical procedure, comorbidities and patient's preference. Postoperative pain management strategies currently used at the MUHC are set with input from pain specialists (Alan Edwards Pain Management Unit) and follow Health Canada standards for safety and efficacy.[26] Examples are included in Figure A1.

To confirm if patients randomized to this group are treated according to current standards of care, we will conduct a retrospective chart review of post-discharge analgesics prescribed to patients who underwent the eligible surgeries between September 01 to October 31, 2019. We estimate that, within this 2-month period, the electronic medical charts of approximately 100 patients will be reviewed. Only data regarding the surgical procedure conducted and analgesia regimen prescribed (pain medication received, dosage, frequency of administration, treatment duration) will be collected by the research team.

Opioid-free (OF) analgesia group

Patients randomized to the OFA group will receive a prescription of around-the-clock non-opioid analgesics (Acetaminophen alone or combined with NSAIDs/COX-2). In case of breakthrough pain, rescue analgesia may be provided by (1) increasing doses of non-opioid analgesics, (2) adding non-opioid drugs that were not included in the initial regimen or (3) switching drugs according to single-dose efficacy evidence [27,28] targeting individual variances in analgesia response.[29] As per standard care, prior to hospital discharge, patients will undergo a medication education session with the PACU nurse and be advised to fill their prescription at a pharmacy of their preference. Considering the pragmatic nature of this trial, the specific non-opioid analgesia regimens will be determined by the patient's primary surgeon considering the surgical procedure, comorbidities and patient's preference. The pain specialists involved in this trial [Dr. Gabriele Baldini (Anesthesia), Dr. Avinash Sinha (Anesthesia), Dr. Suzanne Morin (Internal Medicine), and Ms Krista Brecht (Alan Edwards Pain Management Unit)] have set potential analgesia strategies for the OFA group, according to Health Canada standards for safety and efficacy (Figure A2).[26]

Management of persistent pain

As opioid-free analgesia is new to our setting, specific strategies will be implemented to ensure that patients are receiving adequate pain management during the pilot trial. A 'hotline' (dedicated mobile phone that will be kept with study staff in shifts) will be available 24/7 in case patients experience persistent pain despite the use of rescue analgesia. When this line is called, study staff will inform patients about the management options available according to their treatment allocation. An information sheet containing the 'hotline' contact details will be provided to patients prior to PACU discharge (see **Discharge Information Sheet – Opioid-free Group**).

Patients in the opioid-free group will have a back-up prescription of opioids (regimen decided by the primary surgeon) faxed to the 24h pharmacy closest to their residence. This prescription will be faxed upon patient discharge from the hospital, with a brief letter informing the study and ethics approval (see **Information Sheet for Pharmacy**). When a patient calls the study staff reporting persistent pain, they will be informed about the availability of the prescription and the pharmacy address. To prevent patients to fill their opioid prescription 'just in case', they will not be informed about the availability of the prescription unless they report persistent pain. When the prescription is filled, education about the use of opioids will be given by the pharmacist as per routine pharmacy services. If pain persists despite the use of opioids, patients will be advised to proceed according to the management of persistent pain in the opioid group, as described below.

As per the institutions' current practice, patients in the opioid group who experience persistent pain will be advised to call their primary surgeon's office/clinic during working hours (weekdays, 8AM to 4PM) or visit a hospital emergency room (ER) for further evaluation (after-hours and weekends). If an ER visit is required, patients will be asked to give preference to visiting the ER of the hospital where his/her surgery had been performed. An information sheet containing specific instruction will be provided to patients prior to PACU discharge (see **Discharge Information Sheet – Opioid Group**). Changes of initial prescription will be entirely up to the patients' surgical team and/or ER physician.

Adherence and study discontinuation

Treatment adherence (i.e., patients in each group taking their pain medications as prescribed) will be monitored via self-administered electronic questionnaires distributed using REDCap

(http://project-redcap.org/) and completed by patients via smartphone, tablet or personal computer from postoperative day (POD) 1 to POD 7 and at 2, 3 and 4 weeks after surgery. Electronic adherence data will be transmitted directly to the REDCap database and verified by unblinded study staff. Patients will also be offered the option to respond to adherence questionnaires via telephone; in this case, data will be recorded in paper forms by unblinded staff and subsequently transferred to the REDCap database. Patients will be instructed to take medications for postoperative pain only in accordance to the initial discharge prescription or based on prescriptions given by healthcare providers after hospital discharge. If patients desire discontinuation of any of the study medications, they will be advised to discuss other medication options with the surgical team and/or their outpatient care provider. Surgeons may change pain medications or put an end to a patient participation in the trial at any time if he/she considers this to be in the best interest of the patient.

Other aspects of perioperative care

Surgical techniques, anesthesia procedures, or preoperative/intraoperative analgesia protocols will be left to the discretion of the attending surgeon and anesthesiologist to best reflect routine clinical practice. However, technical details about the surgery, anesthesia and perioperative analgesia interventions (including preoperative use of analgesics in preparation for surgery, e.g., gabapentin, and intraoperative use of local anesthetics infiltration or blocks) will be obtained from electronic medical records and recorded for study purpose. Any nonpharmacological therapies for pain recommended by the surgical team or outpatient healthcare providers (e.g. heat or ice compress, acupuncture, massage therapy) will be permitted and recorded during follow-up assessments. Considering the pragmatic nature of this trial, medication education provided by nurses and all other aspects of perioperative care will be according to the institutions' routine practice, which include detailed care pathways for selected surgical procedures (http://www.muhcpatienteducation.ca/surgery-guides.html).

Measurement Strategy

As a pilot RCT, this study will primarily focus on feasibility outcomes. Clinical outcomes will be assessed secondarily to inform the measurement strategy and sample size requirements for a future full-scale RCT.

Assessment of feasibility outcomes (primary)

A full-scale RCT be deemed feasible if, during the pilot study period (4 months):

- At least 70% of patient undergoing the outpatient general surgery procedures of interest are eligible to be randomized.
- At least 90% of the surgeons who agreed to have their patients randomized will comply with the agreement, i.e. not change their minds (see section 'pilot study sample size and feasibility' below).
- At least 50% of eligible patients agree to participate in the study and are randomized.
- At least 80% of the randomized patients comply with their allocated treatment (i.e. will take their pain medications as prescribed).
- At least 80% of the patients randomized complete outcome assessment at 30-days after surgery.

- Among patients who complete outcome assessments, the proportion of missing data is less than 10% (i.e. non-response to questionnaires or specific questionnaire items).

To determine recruitment rates, study staff will keep a screening log of patients approached, patients who fulfill eligibility criteria and those who do not fulfill eligibility criteria. Reasons for ineligibility will be recorded. This log will also record information about eligible patients who were successfully recruited, and those who were not recruited despite being eligible. In the event of surgeons opting for not recruiting patients despite eligibility, rates and reasons will be recorded. Adherence to treatment will be assessed by comparing patients' analgesia prescription at discharge to self-reported analgesic intake at each time-point of assessment. Follow-up completion rates and missing outcome data will be computed based on REDCap entries (date- and time-stamped). Patients will be considered to have withdrawn from the trial if they miss three consecutive assessments and then permanently stop responding the questionnaires. Reasons for patients not consenting participation, not completing follow-ups or withdrawing from the trial will be recorded whenever possible.

Assessment of clinical outcomes (secondary)

Our clinical outcome measurement strategy was informed by the World Health Organization (WHO)'s International Classification of Functioning and Disability (ICF) and will cover constructs in the domains of impairment, activity limitation and participation restriction.[30] A range of outcome measures were identified as being potentially useful for a full-scale trial on OA versus OFA. One of the main goals for this pilot study is to determine their appropriateness and usability. Due to the subjective nature of pain and response to analgesia, we placed special focus on PROMs, i.e. reports of health status coming directly from the patient. Preference was given to measures that (1) have validity evidence supporting their use in surgical populations,[31,32] (2) have been recommended by surgery, anesthesia and pain societies,[32-34] (3) use scoring systems based on modern psychometric methods (Item-Response Theory, Rasch analysis),[35] (4) have been used in previous literature on postoperative/opioid analgesia, (5) have short recall periods (preferably 24 hours, no more than 7 days) and (6) have low response burden (i.e. are brief). Author-generated questions will be used to assess constructs that have not been addressed by existing measures or that have been addressed in a context that is not applicable to the current study. The outcome measures addressed in this study include: the Brief Pain Inventory Short-Form,[36-38] time to stopping pain medication,[37] Patient-Reported Outcomes Measurement Information System 29 Profile (PROMIS-29); domains: physical function, anxiety, depression, fatigue, sleep disturbance, social roles and activities, pain intensity and pain interference),[33,38,39] Perioperative Opioid-Related Symptom Distress Scale,[40] Prescription Opioid Misuse Index,[41] recovery from surgery (author-generated question), return to work or normal activities (author-generated question), impression of treatment effectiveness (author-generated question), satisfaction with the pain treatment received (author-generated question), 30-day postoperative complications,[42,43] 30-day unplanned healthcare utilization, 30-day adverse drug events,[44-46] and prolonged opioid use (3-month follow-up). See Table A3 for a complete description of these measures.

Patient-reported outcome data will be obtained via (1) electronic questionnaires or (2) telephone interviews, according to the patient's preference. Electronic questionnaires will be completed remotely (via smartphone, tablet or personal computer) using our REDCap platform. A link to the daily questionnaires will be distributed to patients via text message or email (according to the patient's preference) in the morning, with up to 3 reminders sent in case of no response. Participants will be asked to, preferably, complete the questionnaires in the morning to prevent

bias associated to chronobiological variations in pain.[47] Patients who opt for non-electronic assessment will complete the questionnaires via telephone interviews, preferably conducted before 12PM. Information regarding postoperative complications and unplanned healthcare utilization will be obtained via patient self-report (week 4) and verified using electronic medical records. Information regarding opioid prescription dispensing will be obtained using Dossier Santé Québec (DSQ), accessed by a physician-collaborator (Dr. Mohsen Alhashemi, Minimally Invasive Surgery Fellow) upon patient authorization via study consent form. Details of our follow-up schedule are summarized in Figure A4.

Preoperative screening measures

These measures focus on potential prognostic factors for difficult pain control, need for opioid analgesia and opioid seeking behavior after surgery. In a future full-scale RCT, they may help refining inclusion and exclusion criteria, as well as setting stratification strategies to balance important covariates between treatment groups. Screening measures addressed in this pilot study include: demographic and operative information (data also used to characterize the patient population), the Pain Catastrophizing Scale,[48,49] the Pain Anxiety Symptoms Scale (short version),[19,50] the Screener and Opioid Assessment for Patients with Pain (SOAPP),[51] preferred treatment group (author generated question) and expectations for treatment effectiveness (author generated question). See Table A2 for a complete description of these screening measures.

Data management plan and analysis

Data collection and storage will be according to the MUHC's Regulatory Framework in Health Research, which is in line with provincial and federal legislations. All data will be entered and stored in a password-protected system of electronic data capture (REDCap, http://project-redcap.org/) and quality will be ensured via in-built validation checks (i.e., missing data, out-of-range values and invalid responses). Data analysis will be conducted using Stata version 14 software (StataCorp). Analysis and trial reporting will be according to the Consolidated Standards of Reporting Trials (CONSORT) Guidelines extension for Pilot and Feasibility Trials.[52]

Data generated from the pilot study will help inform a full-scale RCT by testing the study procedures; therefore, no inferential statistical analyses will be performed to compare groups. Continuous variables will be summarised using means, standard deviations (SDs), medians, lower and upper quartiles, minimum, maximum and number of observations. Categorical variables will be summarised using frequencies and percentages. To address feasibility, descriptive statistics of patients approached, screened, eligible, consented and randomised, treatment adherence and follow-up completion rates will be computed. Completeness of follow-up will be compared between trial arms. Reasons for non-consent, exclusion and trial withdraw will be recorded and reported. Baseline data will be summarized descriptively to assess comparability between treatment arms and to highlight any differences between patients who were randomized, who withheld consent and who did not meet eligibility criteria. Analyses of postoperative outcomes will be exploratory, descriptive and follow the intention-to-treat principle, with all patients analyzed in their assigned treatment group.

The primary outcome measure to be addressed in the full-scale RCT will be informed by data from this pilot trial. Decision will be based on acceptability and relevance to patients and clinicians (qualitative study described below), completion rates, evidence of measurement properties according to previous literature, effect sizes and sample size requirements. There are no planned interim data analyses; however, if the TMT identifies that recruitment, randomization and data collection are below target, strategies will be implemented to improve progress. Any changes to

methods after trial commencement will be documented and reported. Any future revisions to protocol and consent forms will be implemented only after IRB approval.

Pilot study sample size and feasibility

This pilot trial is not confirmatory; therefore, a formal sample size calculation was not conducted. In accordance to previous recommendation that at least 70 measured participants are required for estimating SDs of continuous measures,[53] we aim to recruit and obtain outcome data from 80 patients (40 per group), allowing for a ~15% attrition rate. This sample size is also in line with recommendations regarding the minimal number of participants required to identify feasibility issues.[54]

This pilot study will be conducted in two high volume centres where approximately 1000 eligible outpatient abdominal and breast surgeries are performed every year. In May 2019, we circulated our study protocol (draft) and conducted an electronic survey of surgeons across the two institution; 10 surgeons (7 General, 3 Breast) agreed to have their patients recruited for this pilot trial. Based on previous trial experience, approximately 60% of the patients approached during the trial period will be eligible and agree to participate. Therefore, we estimate that 80 participants could be feasibly enrolled in 4 months. With additional 3 months required to finalize patient follow-up and the time required for data analyses and report/manuscript preparation, we anticipate that the time required to complete this study is approximately one year. Specific details about our timeline are presented in Figure A4.

PART II. Embedded qualitative study

A qualitative study involving patients and clinicians will be integrated within this pilot trial to provide further fundamental insights into the design of a future full-scale RCT.

Study objective:

The objective of this study is to inform, via qualitative research methods, optimal study design of a full-scale RCT by assessing patient and clinician perspectives on trial conduct, participation, interventions and measurement strategy.

Research questions:

1. What are participants and non-participants' perspectives on the pilot trial conduct, participation (or non-participation), interventions, and measurement strategy?
2. What are clinicians' perspectives on the acceptability of the pilot trial, experience operationalizing the study in practice, treatment effectiveness, challenges that may impact on the feasibility of a full-scale RCT, and areas for improvement in the future trial design?

Interviews will be conducted until thematic saturation is reached (i.e., the point in data collection after which no new themes emerge), accounting for a minimal targeted sample of five patients and five clinicians. Our methodological approach will follow Braun and Clarke's guideline for the use of thematic analysis in qualitative studies.[55] As demonstrated by O'Cathain et al. (2013), qualitative analysis is a valuable tool to optimize interventions in comparative-effectiveness research. Reporting of this qualitative study will be in line with the Consolidated Criteria for Reporting Qualitative Studies (COREQ) guidelines.[56]

Interviews with patients

A sub-sample of patients who participated in the recruitment process for the pilot trial will be invited to participate in one-on-one qualitative interviews. Patients who do not consent to randomization in the trial will also be invited to participate in the interviews as they may provide relevant insights regarding the consent process and study acceptability. In order to capture the heterogeneity of outpatient general surgery procedures and improve sample representativeness, we will use a quota sampling method[57] targeting patients representing a broad spectrum of demographic, clinical and surgical characteristics (Table A10). Patients will be offered the opportunity to be interviewed face-to-face or by telephone. Patients will be informed about the qualitative interviews during preoperative recruitment and those who are interested will be contacted after their involvement with the trial. A consent form specific to the qualitative study will be signed prior to the interviews. To ensure accurate recall, patients will be interviewed no later than 6 weeks after their surgery. Interviews will focus on (1) acceptability of the study, (2) personal experience with the process of recruitment and randomization, (3) reasons for not accepting randomization (where appropriate), (4) perceived value and experiences with the intervention, (5) perceived value and experienced with the outcome assessments, (6) reasons for not completing outcome assessment (where appropriate), and (7) areas for improvement in trial design.

Patient recruitment process

Subsequent contact for participation in the qualitative study will be made upon patient authorization. Patients will be approached as follows, depending on whether they agreed or not to participate in the pilot RCT:

(1) Patients who agreed to participate in the pilot RCT and signed the informed consent form: In the consent form for the Pilot RCT (see " **Informed consent form - Pilot RCT** "), we will ask whether we have permission to contact the patient to inquire about participation in the qualitative part of this project (check "YES" or "NO"). Those who checked “YES” will be contacted after their participation in the Pilot RCT. A separate informed consent form (See "**Informed consent form - Interview with patients**") will be signed prior to the qualitative interview.

(2) Patients who refused to participate in the Pilot RCT: Those who refused to participate in the Pilot RCT will be informed about the qualitative study and be offered to sign a "**Permission to contact form**" if they agree to be contacted regarding participation in the qualitative study. Patient who agree to participate will sign separate informed consent form prior to the qualitative interview (See "**Informed consent form - Interview with patients**").

Interviews with clinicians

A sample of clinicians (surgeons, nurses, anesthesiologists) involved in the perioperative care (i.e. prescription, education about postoperative analgesia) of patients undergoing the surgeries of interest in this trial will be invited to participate in one-on-one qualitative interviews. Interviews will be conducted face-to-face or by telephone after informed consent is obtained. In order to improve sample representativeness, we will use a quota sampling method[57] targeting clinicians representing a broad spectrum of demographic and professional characteristics (Table A11). Interviews will be conducted within the period of patient recruitment to ensure accurate recall. Interviews with clinicians will focus on (1) acceptability of the study, (2) experience operationalizing the study in practice (i.e. recruiting patients and providing interventions), (3) reasons for not recruiting patients (where appropriate), (4) perspectives on treatment effectiveness, (5) local issues that may impact on the feasibility of a full-scale RCT and (6) areas for improvement in trial design.

Clinician recruitment process

All clinicians (surgeons, nurses, anesthesiologists) who care for patients undergoing the surgeries eligible for this study will be informed about the qualitative study by their respective Division Chiefs (see team of collaborators in "Expertise and Resources Available"). Clinicians who meet eligibility criteria will be contacted via email by a member of the study team. Their contact information will be obtained via the McGill and/or MUHC website. Those who agree to participate will sign a consent form (See "**Informed consent form – Interview with Clinicians**") prior to the qualitative interview.

Interview procedures, data management and analysis

Interviews will follow semi-structured guides designed with open-ended questions to elicit patients' and clinicians' personal perspectives about the trial. Initial guides will be drafted by the trial steering committee and pilot tested for terminology, flow and redundancy. All interviews will be digitally recorded using high quality audio equipment and transcribed verbatim by a third-party ISO certified transcription company. Analysis of interview data will be conducted via inductive thematic analysis informed by Braun and Clarke (2006).[55] Thematic analysis is a method used to identify, analyze, and report themes and subthemes within the interviews to provide a rich description of the qualitative data. The inductive approach to thematic analysis is data-driven, where the themes will be derived from within the data themselves and no pre-existing coding framework will be applied during analysis. Based on data obtained from the first interviews, two independent researchers (coders) will code each interview transcription and search for recurring themes. The coding process will be conducted using the software MAXQDA 12 (VERBI GmbH, Berlin, Germany). For every two transcripts coded, coders will meet to (1) compare the codes assigned, (2) revise the codes iteratively as new information emerges, (3) cluster the codes (via thematic mapping) into initial themes and sub-themes to inform the subsequent development and refinement of themes, and 4) generate a clear definition and name for each of the theme. Assessment of saturation will be conducted iteratively (after every 2 interviews) using a saturation grid [58].

The findings from this qualitative study will be regularly fed back to the trial steering committee so that aspects of the pilot study conduct can be reviewed iteratively where appropriate. Themes for which saturation is reached will be classified as meaningful issues to inform the optimal design of the full-scale RCT.

Summary of sample size estimates

PART I. Main study (Pilot RCT)

80 participants (40 per group).

PART II. Embedded qualitative study

20 participants (estimate) - A minimal of 10 participants (5 patients, 5 clinicians) will be recruited but the total sample may vary according to data saturation.

Total sample size

100 participants (estimate).

Expertise and resources available

This project builds on the expertise of scientists and clinicians with extensive experience and knowledge in the fields of surgery and postoperative analgesia. Dr. Julio Fiore Jr (Outcomes Researcher) is the principal investigator and primarily responsible for writing the study protocol. He will be in charge of the overall coordination and supervision of all aspects of this pilot RCT, including recruitment, randomization and data management. He has substantial experience with the design and conduct of pilot and full-scale RCTs. Dr. Gabriele Baldini (Anesthetist) and Dr. Liane Feldman (Surgeon) are co-investigators and knowledge users (i.e. prescribers of postoperative pain medications). They will be responsible for supervising all clinical aspects of the study (i.e. analgesia interventions) and for liaising with clinicians across both study sites. Our team of collaborators bring in a wide range of clinical and research expertise to this project: RCTs (Dr. Kaberi Dasgupta, Physician/Epidemiologist), acute pain assessment and management (Dr. Suzanne Morin, Physician/Epidemiologist), postoperative analgesia (Dr. Avinash Sinha, Anesthetist; Ms Krista Brecht, Pain Nurse), surgery (Dr. Sarkis Meterissian, Breast Clinic Director; Dr. Mohsen Alhashemi, Minimally Invasive Surgery Fellow), opioid misuse (Dr. Marc Martel, Psychologist) and qualitative research (Dr. Fatemeh Rajabiyazdi, Postdoctoral Fellow/Qualitative Researcher). Statistical support from the RI-MUHC Biostatistics Support Unit has been sought and incorporated in this pilot trial in preparation for a full-scale RCT.

The project will be coordinated by the Steinberg-Bernstein Centre for Minimally Invasive Surgery, based at the Montreal General Hospital. The centre offers dedicated office space ($100m^2$) with computer facilities for data collection and warehousing and employs a full-time research coordinator (Ms. Pepa Keneva, MSc). Two master's students (Ms Uyen Do and Mr Charbel El Kefraoui) will coordinate the day-to-day management of the project at the two sites under the supervision of Drs. Fiore, Baldini and Feldman. Our experienced multidisciplinary team has all the necessary elements (i.e. infrastructure, methodological and context expertise) to successfully conclude this project.

Anticipated challenges and mitigation strategies

Prescription of opioids to treat breakthrough pain after surgery is imbedded in Canada' healthcare culture. For this reason, we cannot exclude that (1) certain clinicians may be wary of discharging patients without an opioid prescription and (2) ethical issues may be raised anticipating a negative impact on pain outcomes. However, considering the current opioid crisis, changes have been observed in the paradigm of 'mandatory opioid prescription' as some surgeons across the MUHC began managing pain after outpatient general surgery using only non-opioid drugs. According to their personal experience, this practice did not increase unplanned healthcare visits due to uncontrolled pain and, importantly, satisfaction with pain control reported during scheduled postoperative visits seems unchanged in comparison to when opioids were regularly prescribed. Besides this anecdotal data, preliminary results from our scoping review suggest that previous comparative studies do not support the value of prescribing opioids after outpatient surgery[17-19] – these results, however, must be confirmed in a formal systematic review/meta-analysis. In other patient populations such as chronic musculoskeletal pain and acute extremity pain, the role of opioid analgesia has also recently been questioned in large RCTs showing non-superiority[38,59] and increased adverse events.[38] In light of this evidence and considering the ongoing paradigm change at a local level, this pilot trial gained support from key stakeholders in our surgical departments and divisions who are committed to encouraging recruitment across both study sites.

As certain surgeons may heavily rely on opioids to treat postoperative pain, we anticipate that some may refuse to recruit selected patients or refuse to recruit patients altogether. Similarly, some

patients may be doubtful about the efficacy of pain treatment without opioids and refuse randomization. This issue will be addressed by comparing demographic and surgical data of randomized patients versus non-randomized patients. Differences may suggest that our results are not generalizable to certain surgical populations, indicating venues to improve our patient selection criteria and/or recruitment process. Our integrated qualitative study including interviews with patients who refused randomization and surgeons with low recruitment rates will provide fundamental insights into the strategies to mitigate these potential issues. The qualitative study will also provide relevant information to optimize our measurement strategy, which currently includes daily follow-up in the first 7 days after surgery. The use of daily outpatient follow-up assessment has been successful in a recent RCT on postoperative analgesia[37] but, if proven unfeasible in our setting, strategies will be implemented to reduce patient burden (e.g. reducing follow-up frequency).

Finally, surgeons from different specialities may give preference to different non-opioid drugs, e.g. NSAIDs/COX-2 may be avoided by some surgeons due to potential risk of bleeding,[60] while others may be concerned about risk of liver failure when using acetaminophen.[61] In line with the pragmatic nature of this trial, surgeons will have the freedom to, within the analgesia principles of each intervention group, choose the regimen that they find most appropriate according to surgical procedure, comorbidities and individual preference. To ensure safety, analgesia prescriptions will follow Health Canada monographs for maximum dosages and length of treatment.[26] Potential treatment adverse events will be identified and reported according to internationally accepted standards supported by Health Canada.[44-46,62]

Data Collection and Confidentiality

Retrospective chart review: All the information collected during our preliminary chart review will remain confidential to the extent required and provided by law. A study ID number will be assigned to each patient's chart. No code linking patient identifiers to patient data will be kept and it will not be possible to identify patients.

Pilot Trial: All data collected in our pilot trial will be entered and stored in a password-protected system of electronic data capture (REDCap; Research Electronic Data Capture, hosted at Research Institute of MUHC), and subsequently transferred to the statistical program for analysis. A study ID number will be assigned to each participant. Information collected in paper-based forms will be kept in locked cabinets within a locked office (R2-111). Participants will be identified by a code to protect their identity. A document linking the codes to the participants' identity will be kept separately in a password protected file, which can only be accessed by the study staff.

All data will be kept under safe storage for 7 years and then deleted, shredded or incinerated. Only investigators will have access to the data. Furthermore, the results and the project may be published, but patients' identity will not be revealed.

Knowledge translation (KT) plan

Results from this pilot trial will inform the planning and commissioning of a future full-scale RCT on opioid-free analgesia after outpatient general surgery. If proven feasible, this full-scale RCT will inform guidelines targeting sustainable changes in surgical care to mitigate the negative downstream effects of postoperative opioid overprescription. Our findings will be disseminated according to CIHR's Guide to Knowledge Translation (KT) Planning[63] and target a broad audience of surgeons, anesthetists, nurses, pharmacists, surgical outcomes scientists and research funders. Our KT strategies include, but are not limited to, conference presentations (local, national and

international), publication of a peer-reviewed paper, and diffusion of findings in websites, newsletters and social media platforms. As opioids are part of standard postoperative care in North America, we believe that our study will contribute feasibility data to support and encourage further opioid-free analgesia research beyond our immediate research setting in Canada and internationally (i.e. the United States).

Significance

The overprescription of opioids to surgical patients is recognized as one of the driving forces behind the current opioid crisis. Patients undergoing outpatient general surgery are frequently prescribed opioids to be taken at home postoperatively, but this practice is not supported by evidence. Alternatives to opioids are often overlooked by Canadian surgeons, while they should be incorporated as the foundation of postoperative analgesia whenever possible. If proven effective in a future full-scale RCT, the use of opioid-free analgesia after outpatient surgery may ultimately contribute to preventing opioid-related harms. Hence, the pilot study described in this protocol is an essential first step for building a strong body of evidence to mitigate the negative downstream effects of postoperative opioid overprescription in Canada.

AMENDMENTS TO THE PROTOCOL AFTER INITIAL ETHICS APPROVAL

Change	Reason
October 2019. Prior to patient recruitment ***Retrospective chart review***	• To confirm that patients randomized to OA group are treated according to current standards of care, a retrospective chart review was conducted to collect data on post-discharge analgesics prescribed to patients who underwent the eligible surgeries in 2019 [period of January 01 to December 31, 2019]. This data (not reported in the manuscript) supported that patients in the OA group were treated according to standard care.
October 2019. Prior to patient recruitment ***Randomization strategy***	• After discussion with surgeons, the team realized that the randomization of patients in the PACU (with discharge prescriptions written right before hospital discharge) would be impractical as surgeons often write their prescriptions in the OR after skin closure. For this reason, randomizations were conducted in the OR.
September 2020. After patient recruitment ***Knowledge translation plan***	• After discussion, the team decided that the two components of this pilot study (quantitative and qualitative) would be reported in separate manuscripts.
June 2021. After patient recruitment ***Outcome measure/data analysis*** Data on overall impression of treatment effectiveness at each postoperative timepoint.	• We noticed that this author-generated question was accidently excluded from the final version of the Redcap questionnaire distributed to patients. Therefore, these data were not analyzed or reported in the manuscript. Impressions about treatment effectiveness were detected via other patient-reported questionnaires.
June 2021. After patient recruitment and data analysis ***Outcome measure/data analysis*** Data regarding satisfaction with pain management at postoperative week 4	• After data analyses, the team realized that findings regarding satisfaction with pain management at postoperative week 4 were redundant (did not add relevant information in comparison to the data reported by patients on week 1). For this reason, this information was not reported in the manuscript. This data would not be useful as it is subject to recall bias given that most patients do not use pain medications beyond week 1.

Table A1. CONSORT 2010 statement: extension to randomised pilot and feasibility trials

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	28
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	Abstract p. 30-31
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	32
	2b	Specific objectives or research questions for pilot trial	32
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	33
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	Appendix (Amendments)
Participants	4a	Eligibility criteria for participants	33
	4b	Settings and locations where the data were collected	33
	4c	How participants were identified and consented	33
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	34-35
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	35-37
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	Appendix (Amendments)
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	36
Sample size	7a	Rationale for numbers in the pilot trial	37-38
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	33
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	33
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	34

Section/Topic	Item No	Checklist item	Reported on page No
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	33-34
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	33-34
	11b	If relevant, description of the similarity of interventions	34-35
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	Figure 2-1
	13b	For each group, losses and exclusions after randomisation, together with reasons	38-39
Recruitment	14a	Dates defining the periods of recruitment and follow-up	38
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2-2
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	Included in all tables and figures
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Figure 2-2 Table 2-3
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial – include MID	Figure 2-2
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	46
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	48
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	48
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	46-48
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	46-48, Appendix (Amendments)

Section/Topic	Item No	Checklist item	Reported on page No
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	33
Protocol	24	Where the pilot trial protocol can be accessed, if available	Appendix (Study protocol)
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	29
	26	Ethical approval or approval by research review committee, confirmed with reference number	32

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.
*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

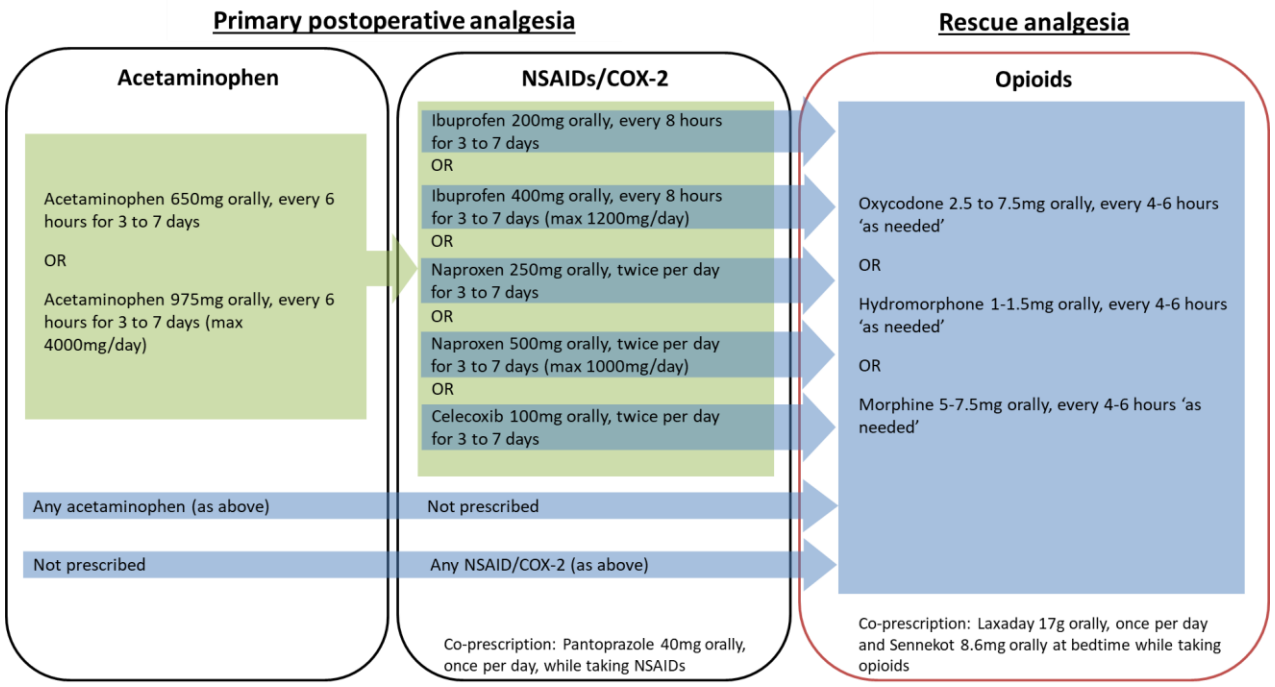


Figure A1. Postoperative analgesia regimens for Opioid Analgesia (OA) group.

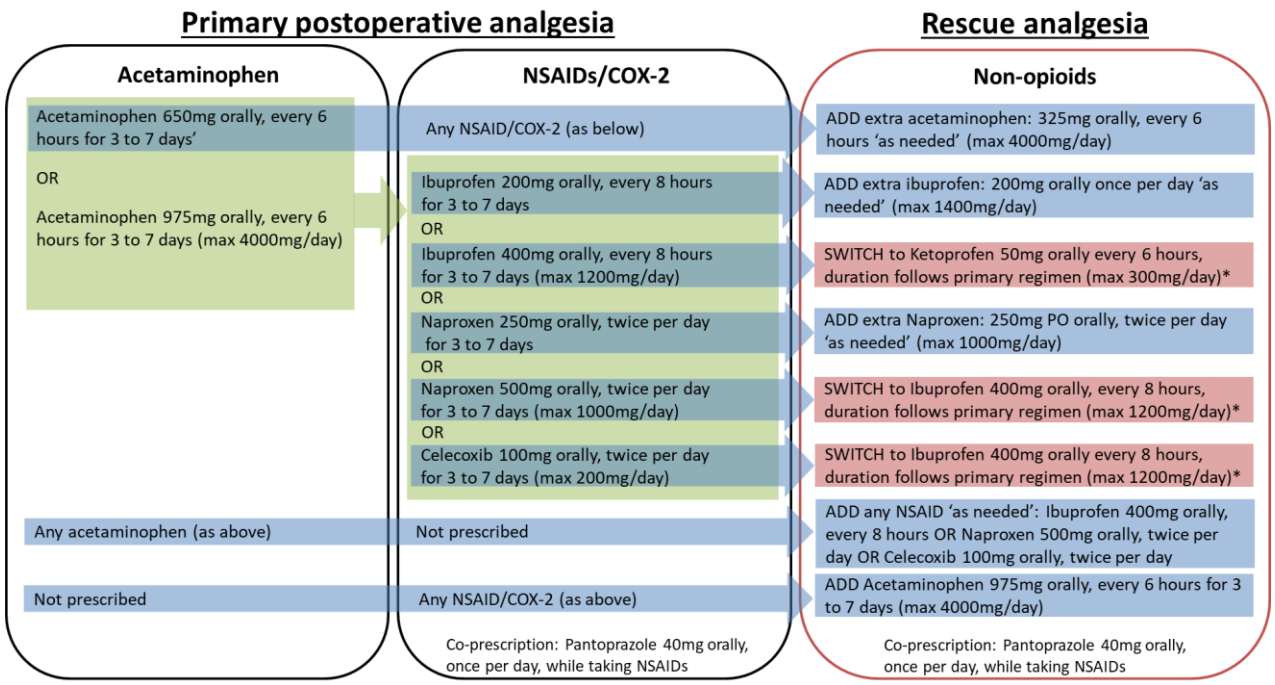


Figure A2. Postoperative analgesia regimens for Opioid-Free Analgesia (OFA) group.

*Drug switching informed by single-dose efficacy evidence [27,28] targeting individual variances in analgesia Response.[29] Ketoprofen is not routinely used as primary analgesia and will only be used as a rescue.

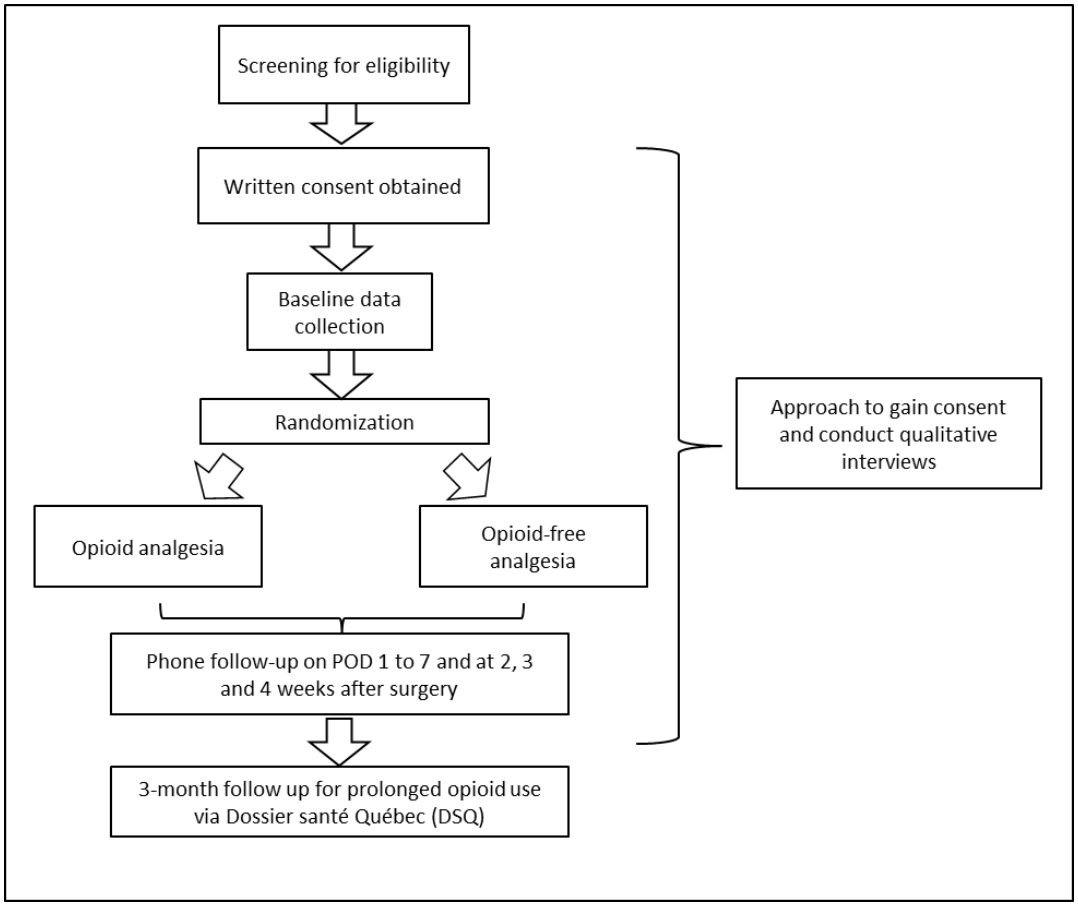


Figure A3. Flow of participants through the study. POD = postoperative day

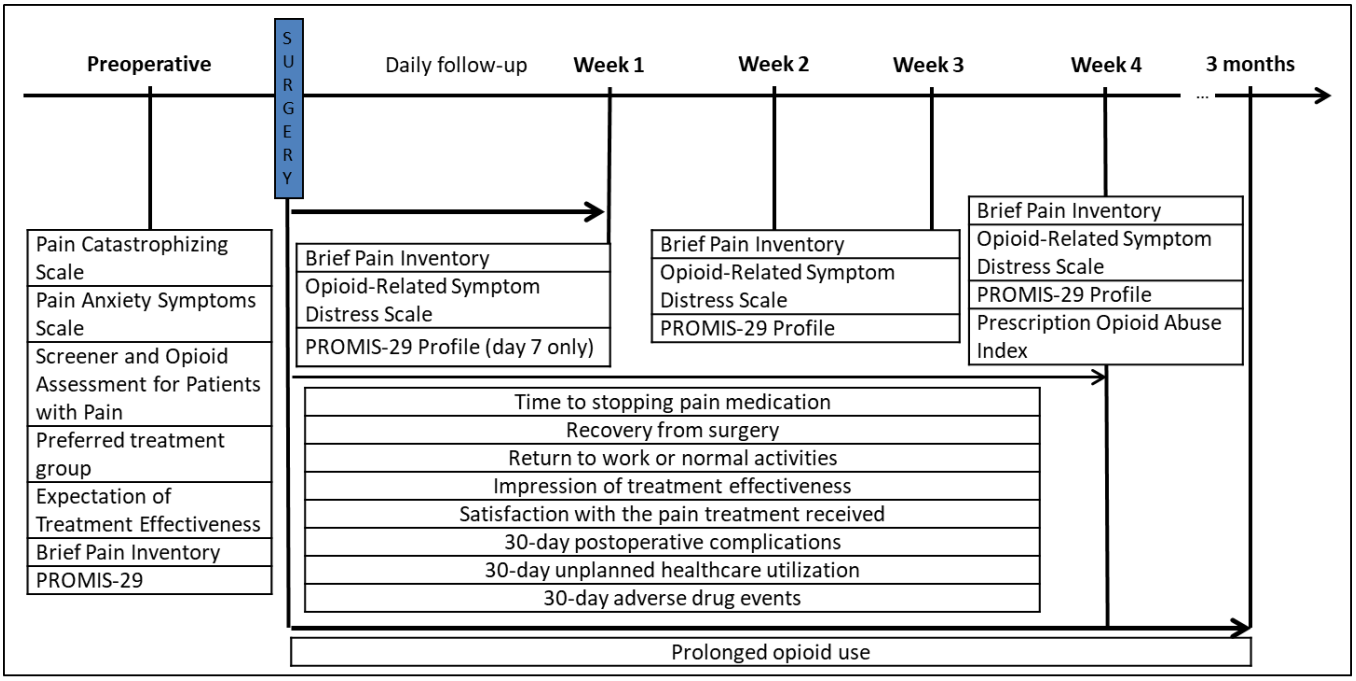


Figure A4. Patient follow-up schedule, POD = Postoperative day

Table A2. Screening measures: Constructs targeted, corresponding measures (or sources of data) and description

Target construct	Measure/data source	Description
Demographic and operative information	Data obtained from electronic medical records	Patient demographics and information relevant to the surgical procedure was obtained from electronic medical records. This included: age, sex, gender, BMI, diagnosis, American Society of Anesthesiologists (ASA) score, surgery performed, technical details, anesthesia information (i.e., use of local infiltrations, blocks and other adjuncts), surgery duration, transfusion requirements, intraoperative and early postoperative complications.
Pain Catastrophizing	Pain Catastrophizing Scale [48,49]	This 13-item questionnaire (5-point scale, 0= "not at all", 4= "all the time") aims to quantify an individual's tendency to magnify the threat value of pain and to feel helpless in its presence. The recall period is not specific ('when you are experiencing pain…'). Scoring algorithms provide a total pain catastrophizing score (range 0-52, best-worst), as well as subscale scores (rumination, magnification and helplessness). This questionnaire was administered only preoperatively.
Risk for opioid-related aberrant behaviors	Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1.0-SF [51]	This 5-item self-reported questionnaire was designed to predict aberrant medication-related behaviors among pain patients considered for opioid therapy. Questions focus on history of substance abuse, legal problems, craving medication, heavy smoking, and mood swings. A score of 4 or above indicate high risk of opioid abuse after prescription. This questionnaire was administered only preoperatively.
Preferred treatment group	Author-generated question	Patients were asked to state their preferred treatment group using an author-generated question (response options: pain treatment using opioids/pain treatment not using opioids/no preference). Patients responded to this question only preoperatively.
Expectation for treatment effectiveness	Author-generated question	Using an author-generated question, patients were asked to state their expectation of treatment effectiveness for pain treatment using opioids and not using opioids (response options: not effective/somewhat effective/very effective). Patients responded to this question only preoperatively.

BMI = Body Mass Index.

Table A3. Outcome measures: Constructs targeted, corresponding measures (or sources of data) and description

Target construct	Measure/data source	Description
Pain intensity Pain interference	Brief Pain Inventory Short-Form [36-38]	This is a 9-item questionnaire that addresses pain severity (11-point scale, 0=”no pain”, 10= “worst pain imaginable”) in the last 24 hours. The questionnaire also inquires about pain location, impact of pain on daily function, pain medications (types and amount) and experienced of pain relief. Pain intensity score was calculated as the average of pain at its “worst”, “least”, “average”, and “now” (current pain). Pain interference score was calculated as the average of 7 items: general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. This questionnaire was administered preoperatively (also as a screening measure), on POD 1 to 7 and at 2, 3 and 4 weeks after surgery. Modifications: (1) the diagram indicating pain location was excluded (patients were specifically inquired about pain around the surgical incision(s)) and (2) The item inquiring about the use of specific pain medications, which may unblind assessors to group allocation, was excluded.
Time to stopping pain medication	Brief Pain Inventory Short-Form [37]	The time to the first report of stopping the use of pain medication was calculated based on information obtained via treatment adherence telephone follow-ups (assessment not blinded). For follow-ups on POD 1 to POD 7, the time to stopping pain medication was calculated based on the first of two consecutive reports of ‘no pain medication’. If pain treatment continued beyond POD 7, patients were asked to recall the last day of pain medication use at 2, 3 and 4 weeks after surgery, as appropriate.
Physical function Anxiety Depression Fatigue Sleep disturbance Social roles and activities Pain intensity Pain interference	PROMIS-29 Physical function PROMIS-29 Anxiety PROMIS-29 Depression PROMIS-29 Fatigue PROMIS-29 Sleep disturbance PROMIS-29 Social roles and activities PROMIS-29 Pain intensity PROMIS-29 Pain interference [33,38,39]	This generic health-related quality of life survey, derived from the US National Institutes of Health (NIH) PROMIS item bank, assesses 7 domains of health (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference). It contains 29 items, including four items from each primary domain (5-point scale, ranging from 1 to 5, with different response options for different domains) plus a single item for pain intensity rating (11-point rating scale, where 0=no pain and 10=worst imaginable pain). Recall periods vary between domains (7 days or non-specific). Higher scores indicate more of the particular scale’s domains, which may represent a desirable outcome (e.g., higher scores for the Physical Function scale represent better function) or an undesirable outcome (e.g., higher scores on the Depression scale indicate more depressive symptoms). Scoring is based on item-response theory. Raw scores are calculated separately for each domain and expressed as T-scores, representing a standardized score with a mean of 50 (corresponding to the mean score in the US general population) and a standard deviation (SD) of 10. This questionnaire was administered preoperatively (also as a screening measure), on POD 7 and at 2, 3 and 4 weeks after surgery.
Opioid side effects	Perioperative Opioid-Related Symptom Distress Scale [40]	This 10-item questionnaire measures symptom distress due to common adverse effects experienced by patients who receive opioids to relieve postoperative pain (fatigue, drowsiness, inability to concentrate, confusion, nausea, dizziness, constipation, itching, difficulty with urination, and retching/vomiting). These adverse effects are assessed across 3 distress dimensions: frequency (‘rarely’ to ‘almost constantly’), severity (‘slight’ to ‘very severe’) and degree of bother (‘not at all’ to ‘very much’). The recall period is 24 hours. We calculated a composite score based on clinically meaningful events as published by Chan et al, as well individual scores for

Target construct	Measure/data source	Description
		each symptom. This questionnaire was administered on POD 7 and at 2, 3 and 4 weeks after surgery.
Opioid misuse	Prescription Opioid Abuse Index [41]	This 6-item questionnaire includes questions regarding excessive dose, frequency of use, need for early refills, feeling high from the medication, taking the medication due to stress and obtaining prescriptions from multiple physicians. An affirmative answer to more than one question correctly classified an individual as an opioid misuser. This questionnaire was administered at 4 weeks after surgery.
30-day postoperative complications	Data obtained from electronic medical records	Data regarding postoperative complications was obtained from medical records and graded by severity using the Clavien-Dindo classification.[42] This system grades complications according to the therapy needed for treatment (grades I to IV, best to worse). Complications within 30 days after surgery were recorded. In addition, the Comprehensive Complication Index (CCI) was generated for each patient to summarize the complete spectrum of postoperative complications and their severity in a single score ranging from 0 to 100 (best to worse) [43].
30-day unplanned healthcare utilization	Data on obtained from the electronic medical records and verified with patients via phone follow-up	Unplanned healthcare utilization (ED visits and unplanned hospital readmissions) within 30 days after surgery was extracted from the electronic medical records and verified with patients via phone follow-up. Patients were also be inquired about ED visits and admissions to non-MUHC sites, as well as emergency visits to outpatient care providers (i.e., family doctor, walk in-clinics, surgery clinic).
30-day adverse drug events	Data obtained from spontaneous patient reporting and electronic medical records	Data regarding adverse drug events was obtained from spontaneous patient reporting (Trigger question "Did you have any significant medical problem related or unrelated to your surgery since the last study assessment?") and from data reported by clinicians in electronic medical records. Two independent clinicians, blinded to treatment allocation, will code adverse event data using the MedDRA coding dictionary [44].Disagreements regarding coding, were resolved by consensus. Adverse drug events were monitored up to 30 days after surgery.
Prolonged opioid use (3-month follow up)	Data obtained via the Dossier Santé Québec	Requirement for extra opioid prescriptions was monitored for 3 months via the Dossier Santé Québec, which is a province-wide electronic health information system that includes drug prescriptions received in hospitals and outpatient settings. The percentage of patients receiving opioids was calculated weekly in the first month, and then monthly until the 3rd month after surgery.
Recovery from surgery	Author-generated question	Patients were asked whether they consider themselves to be completely recovered from the surgery (response options: yes/no). Patients responded to this question at 4 weeks after surgery. Time to complete recovery was calculated based on the difference (in days) between date perceived of feeling fully recovered and surgery date.
Return to work or normal activities	Author-generated question	Patients were asked whether they have returned to work (any vocational activity, paid or not paid) or, if unemployed or retired, if they returned to pre-operative levels of activity (response options: yes/no). Patients responded to this question at 4 weeks after surgery.
Overall impression of treatment effectiveness	Author-generated question	Patients were asked to state their overall impression about the effectiveness of the pain treatment that they are receiving (response options: not effective/somewhat effective/very effective). Patients responded to this question at each postoperative time-point, until they reported having stopped using pain medication.
Overall satisfaction with the pain treatment received	Author-generated question	Patients were asked to rate their overall satisfaction with the pain treatment that they received (response options: very dissatisfied /dissatisfied/satisfied/very satisfied). Patients responded to this question

Target construct	Measure/data source	Description
		when they report having stopped using pain medication or at 4 weeks after surgery, whichever comes first.

WHO = World Health Organization, MedDRA = Medical Dictionary for Regulatory Activities, CTCAE = Common Terminology Criteria for Adverse Events, WHO/UMC = World Health Organization/Uppsala Monitoring Centre, PROMIS = Patient-Reported Outcomes Measurement Information System.

Table A4. Relevant baseline and operative characteristics of eligible patients who consented and did not consent participation

	Eligible and consented (n=76)	Eligible and did not consent (n=70)	p-value
Age, mean (SD), y	55.5 (14.5)	57.9 (14.6)	0.32
≥ 75 years old	5 (7)	6 (9)	0.65
Female	50 (66)	41 (59)	0.37
BMI, mean (SD)[a]	27.6 (7.0)[b]	26.6 (5.1)[b]	0.36
≥ 30.0	18 (25)[b]	11 (16)[b]	0.18
Physical status (ASA)			
I	15 (20)	11 (16)	0.58
II	53 (70)	53 (78)	0.26
III	8 (10)	4 (6)	0.31
Current smoker	13 (18)[c]	11 (16)	0.77
Current at-risk alcohol use[e]	5 (7)	8 (11)	0.33
Previous surgery	65 (86)	53 (76)[d]	0.18
Abdominal surgery	40 (53)	35 (50)	0.75
Laparoscopic appendectomy	1 (1)	1 (1)	0.95
Laparoscopic cholecystectomy	9 (12)	8 (11)[f]	0.94
Laparoscopic inguinal hernia repair	9 (12)[f]	6 (9)	0.52
Laparoscopic incisional hernia repair	0 (0)	1 (1)	0.30
Open inguinal hernia repair	17 (22)	16 (23)	0.94
Open umbilical hernia repair	3 (4)	3 (4)	0.92
Open incisional hernia repair	1 (1)	0 (0)	0.34
Breast surgery	36 (47)	35 (50)	0.75
Partial mastectomy	14 (18)	13 (19)	0.98
Partial mastectomy with sentinel node biopsy	11 (14)	6 (9)	0.27
Partial mastectomy with axillary node dissection	6 (8)	9 (13)	0.33
Partial mastectomy with reconstruction	0 (0)	1 (1)	0.30
Partial mastectomy with sentinel node biopsy and reconstruction	1 (1)	1 (1)	0.95
Total mastectomy with sentinel node biopsy	2 (3)	1 (1)	0.61
Total mastectomy with sentinel node biopsy and reconstruction	1 (1)	2 (3)	0.51
Total mastectomy with axillary node dissection and reconstruction	1 (1)	2 (3)	0.51
Duration of surgery (minutes)	91±45	94±46[c]	0.68
Received intraoperative regional analgesia			

Peripheral nerve block	11 (14)	14 (20)	0.38
Local infiltration	57 (75)	56 (80)	0.47

Data are n (%), median (IQR) or mean±SD. Continuous variables compared using Mann–Whitney U test and categorical variables compared using Chi-square test. BMI=body mass index; ASA=American Society of Anesthesiologists

[a] Calculated as weight in kilograms divided by square of heights in meters.

[b] Missing data for 3 patients.

[c] Missing data for 2 patients.

[d] Missing data for 1 patient.

[e] Alcohol consumption above Canada's Low-Risk Alcohol Drinking Guidelines (2017) for men (>15 standard drinks per week) and women (>10 standard drinks per week) [64].

[f] Includes one patient who had an open umbilical hernia repair during the same procedure.

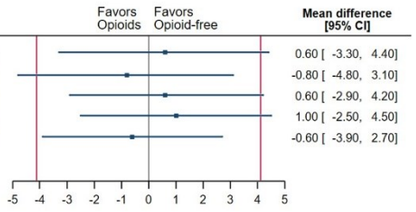
Table A5. Comparison between the outcome assessors' guesses about allocation (opioid vs. opioid-free analgesia) and actual allocation at postoperative week 4 after surgery

	Opioid analgesia	Opioid-free analgesia
Correct guess	19/39 (49)	18/37 (49)
Incorrect guess	20/39 (51)	19/37 (51)

Data are number of correct guesses/total number of guesses (%).

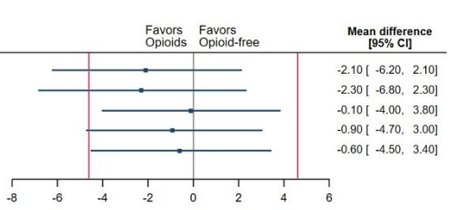
A. Physical functioning

Timepoint	Opioid-free analgesia Mean	SD	Median	IQR	Range	Opioid analgesia Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	50.8	8.6	57.0	[46.1 - 57.0]	[30.6 - 57.0]	50.2	8.3	57.0	[43.3 - 57.0]	[31.1 - 57.0]	0.60 [-3.30, 4.40]
POW 1	44.1	9.1	44.6	[38.4 - 47.8]	[22.6 - 57.0]	44.9	8.3	44.6	[39.8 - 47.8]	[27.9 - 57.0]	-0.80 [-4.80, 3.10]
POW 2	47.9	8.1	47.8	[42.9 - 57.0]	[27.7 - 57.0]	47.2	7.5	45.7	[41.6 - 57.0]	[32.5 - 57.0]	0.60 [-2.90, 4.20]
POW 3	50.6	7.3	56.3	[45.1 - 57.0]	[35.5 - 57.0]	49.6	7.7	48.1	[42.9 - 57.0]	[34.5 - 57.0]	1.00 [-2.50, 4.50]
POW 4	51.5	7.2	57.0	[46.1 - 57.0]	[37.2 - 57.0]	52.1	7.0	57.0	[45.1 - 57.0]	[36.9 - 57.0]	-0.60 [-3.90, 2.70]



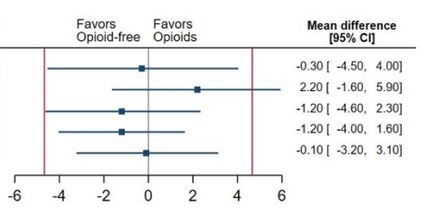
B. Social participation

Timepoint	Opioid-free analgesia Mean	SD	Median	IQR	Range	Opioid analgesia Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	52.9	8.7	52.2	[46.1 - 58.5]	[32.9 - 64.2]	55.0	9.4	57.5	[48.2 - 64.2]	[38.5 - 64.2]	-2.10 [-6.20, 2.10]
POW 1	47.3	10.4	46.1	[42.2 - 51.8]	[27.5 - 64.2]	49.6	9.6	50.2	[41.8 - 58.1]	[31.6 - 64.2]	-2.30 [-6.80, 2.30]
POW 2	54.4	8.3	55.5	[49.5 - 64.2]	[37.2 - 64.2]	54.5	8.8	55.9	[44.8 - 64.2]	[38.6 - 64.2]	-0.10 [-4.00, 3.80]
POW 3	55.6	8.6	57.5	[48.3 - 64.2]	[37.4 - 64.2]	56.5	8.0	57.5	[50.1 - 64.2]	[37.2 - 64.2]	-0.90 [-4.70, 3.00]
POW 4	56.6	8.4	58.4	[51.8 - 64.2]	[37.8 - 64.2]	57.2	8.4	58.5	[51.6 - 64.2]	[35.1 - 64.2]	-0.60 [-4.50, 3.40]



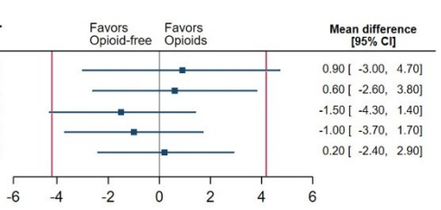
C. Anxiety

Timepoint	Opioid-free analgesia Mean	SD	Median	IQR	Range	Opioid analgesia Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	53.0	8.5	53.6	[48.1 - 61.3]	[40.3 - 69.5]	53.3	9.9	56.0	[40.3 - 60.0]	[40.3 - 71.4]	-0.30 [-4.50, 4.00]
POW 1	48.6	8.0	49.0	[40.3 - 55.8]	[40.3 - 68.1]	46.4	8.4	40.3	[40.3 - 55.3]	[40.3 - 65.1]	2.20 [-1.60, 5.90]
POW 2	44.7	6.9	40.3	[40.3 - 50.4]	[40.3 - 63.5]	45.9	8.1	40.3	[40.3 - 51.4]	[40.3 - 65.2]	-1.20 [-4.60, 2.30]
POW 3	43.2	5.6	40.3	[40.3 - 40.7]	[40.3 - 58.0]	44.4	6.4	40.3	[40.3 - 48.2]	[40.3 - 59.7]	-1.20 [-4.00, 1.60]
POW 4	44.4	6.7	40.3	[40.3 - 48.1]	[40.3 - 57.9]	44.5	6.7	40.3	[40.3 - 48.2]	[40.3 - 63.5]	-0.10 [-3.20, 3.10]



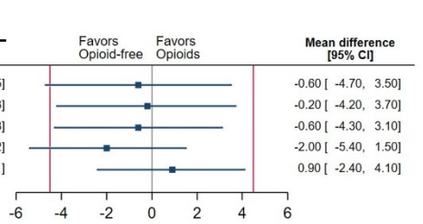
D. Depression

Timepoint	Opioid-free analgesia Mean	SD	Median	IQR	Range	Opioid analgesia Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	48.0	8.2	41.0	[41.0 - 55.9]	[41.0 - 69.5]	47.1	8.7	41.0	[41.0 - 54.1]	[41.0 - 67.5]	0.90 [-3.00, 4.70]
POW 1	46.2	7.2	41.0	[41.0 - 49.3]	[41.0 - 62.2]	45.6	6.8	41.0	[41.0 - 49.1]	[41.0 - 60.6]	0.60 [-2.60, 3.80]
POW 2	43.6	5.8	41.0	[41.0 - 41.0]	[41.0 - 62.2]	45.1	6.7	41.0	[41.0 - 49.8]	[41.0 - 62.2]	-1.50 [-4.30, 1.40]
POW 3	43.7	5.0	41.0	[41.0 - 49.8]	[41.0 - 57.5]	44.7	6.4	41.0	[41.0 - 49.8]	[41.0 - 60.6]	-1.00 [-3.70, 1.70]
POW 4	44.3	6.0	41.0	[41.0 - 48.9]	[41.0 - 58.7]	44.1	5.3	41.0	[41.0 - 48.9]	[41.0 - 57.5]	0.20 [-2.40, 2.90]



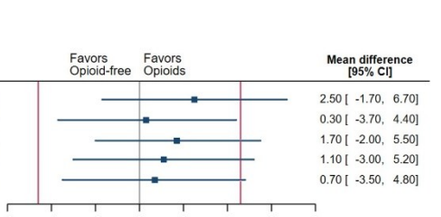
E. Pain interference

Timepoint	Opioid-free analgesia Mean	SD	Median	IQR	Range	Opioid analgesia Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	48.4	8.9	41.6	[41.6 - 68.9]	[41.6 - 68.9]	49.1	9.0	41.6	[41.6 - 65.5]	[41.6 - 65.5]	-0.60 [-4.70, 3.50]
POW 1	55.5	9.1	55.7	[52.2 - 61.3]	[41.6 - 75.6]	55.7	8.3	55.7	[51.7 - 61.3]	[41.6 - 71.3]	-0.20 [-4.20, 3.70]
POW 2	49.9	7.1	52.4	[41.6 - 54.9]	[41.6 - 61.3]	50.5	8.9	51.7	[41.6 - 57.5]	[41.6 - 67.8]	-0.60 [-4.30, 3.10]
POW 3	46.5	7.3	41.6	[41.6 - 53.9]	[41.6 - 64.7]	48.5	7.6	41.6	[41.6 - 55.7]	[41.6 - 65.2]	-2.00 [-5.40, 1.50]
POW 4	46.7	7.1	41.6	[41.6 - 52.4]	[41.6 - 62.3]	45.9	6.8	41.6	[41.6 - 51.7]	[41.6 - 61.1]	0.90 [-2.40, 4.10]



F. Sleep disturbance

Timepoint	Opioid-free analgesia Mean	SD	Median	IQR	Range	Opioid analgesia Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	49.3	8.6	52.1	[46.4 - 54.5]	[32.0 - 62.1]	46.8	9.8	46.4	[41.2 - 51.4]	[32.0 - 69.4]	2.50 [-1.70, 6.70]
POW 1	47.4	9.1	46.4	[42.1 - 52.8]	[32.0 - 69.4]	47.1	8.5	46.4	[41.2 - 53.3]	[32.0 - 63.8]	0.30 [-3.70, 4.40]
POW 2	46.9	9.0	47.2	[41.2 - 52.8]	[32.0 - 63.8]	45.2	7.5	46.3	[41.2 - 49.6]	[32.0 - 58.7]	1.70 [-2.00, 5.50]
POW 3	46.1	9.3	48.3	[40.0 - 53.3]	[32.0 - 60.6]	45.0	8.3	43.8	[38.4 - 51.1]	[32.0 - 62.0]	1.10 [-3.00, 5.20]
POW 4	44.3	9.3	45.3	[32.0 - 49.6]	[32.0 - 63.4]	43.6	8.5	44.1	[36.9 - 51.1]	[32.0 - 61.9]	0.70 [-3.50, 4.80]



G. Fatigue

Timepoint	Opioid-free analgesia Mean	SD	Median	IQR	Range	Opioid analgesia Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	47.7	10.0	48.6	[39.7 - 57.1]	[33.7 - 64.7]	45.9	9.5	46.0	[33.7 - 53.2]	[33.7 - 66.6]	1.80 [-2.70, 6.20]
POW 1	50.2	11.2	48.6	[43.1 - 57.1]	[33.7 - 75.8]	48.4	9.4	48.6	[43.1 - 53.2]	[33.7 - 71.5]	1.80 [-2.90, 6.60]
POW 2	44.6	10.3	46.0	[33.7 - 48.6]	[33.7 - 64.7]	43.0	9.6	43.1	[33.7 - 51.0]	[33.7 - 62.7]	1.60 [-2.90, 6.20]
POW 3	42.4	9.9	39.8	[33.7 - 48.6]	[33.7 - 64.7]	41.8	8.2	40.6	[33.7 - 48.6]	[33.7 - 57.1]	0.60 [-3.60, 4.80]
POW 4	42.2	9.8	36.7	[33.7 - 48.6]	[33.7 - 64.8]	40.9	7.7	39.8	[33.7 - 48.6]	[33.7 - 55.2]	1.20 [-2.90, 5.30]

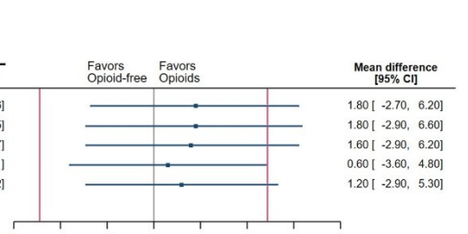


Figure A5. Between-group differences in the PROMIS-29 domains T-scores.

Red lines represent minimal clinically important differences (MCID) (MCIDs were estimated as 0.5 standard deviation at baseline for each domain [65]). Missing follow-up data: POW3 n = 2, POW4 n = 3. Higher scores on physical function and social participation domains indicate desirable outcomes. Higher scores on anxiety, depression, pain interference, sleep disturbance, and fatigue domains indicate undesirable outcomes. Pain intensity scores are not based on the same unit of measure of the other domains (T-scores) and, therefore, are not included in the graph. PROMIS-29 pain intensity data are reported in the table below.

PROMIS-29® pain intensity scores[a]

	Opioid analgesia (n=39)			Opioid-free analgesia (n=37)			Between-group difference (95%CI)[b]
	Mean (SD)	Median (IQR)	Range (max – min)	Mean (SD)	Median (IQR)	Range (max – min)	
Baseline	2.2 (2.5)	1 (0-4)	9 (0-9)	2.2 (2.6)	2 (0-3)	8 (0-8)	0.1 (-1.1 to 1.2)
Postoperative week 1	2.5 (1.9)	2 (1-4)	7 (0-7)	2.7 (2.1)	3 (1-4)	7 (0-7)	0.2 (-0.7 to 1.1)
Postoperative week 2	1.5 (1.7)	1 (0-2)	6 (0-6)	1.2 (1.4)	1 (0-2)	6 (0-6)	-0.3 (-1.0 to 0.4)
Postoperative week 3	0.8 (1.2)	0 (0-2)	5 (0-5)	1.0 (1.4)	1 (0-1)	6 (0-6)	0.2 (-0.5 to 0.8)
Postoperative week 4	0.7 (1.4)	0 (0-1)	7 (0-7)	0.8 (1.1)	0 (0-1)	5 (0-5)	0.1 (-0.6 to 0.6)

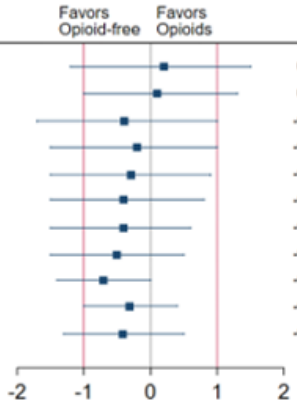
Data are mean (SD). PROMIS® = Patient-Reported Outcomes Measurement Information System. POW3 OFA n =35; POW4 OFA n = 34 (due to losses of follow-up).

[a] Pain intensity rating is a 11-point rating scale (range, 0-10; 0 = no pain and 10 = worst imaginable pain). Recall period is 7 days.

[b] Between-group difference represents mean difference

A. Pain intensity

	Opioid-free analgesia					Opioid analgesia					
Timepoint	Mean	SD	Median	IQR	Range	Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	1.4	2.4	0	[0 - 2.3]	[0 - 6.8]	1.3	1.9	0	[0 - 2.8]	[0 - 5.0]	0.20 [-1.20, 1.50]
POD 1	3.3	1.6	3.4	[2.4 - 4.4]	[0 - 6.3]	3.2	2.0	3.8	[2.0 - 4.8]	[0 - 6.5]	0.10 [-1.00, 1.30]
POD 2	2.8	2.1	2.5	[1.5 - 4.6]	[0 - 6.3]	3.2	2.1	3.6	[1.9 - 4.8]	[0 - 7.5]	-0.40 [-1.70, 1.00]
POD 3	2.2	2.0	2.0	[0.3 - 3.5]	[0 - 6.3]	2.5	2.1	2.1	[0.9 - 4.0]	[0 - 7.0]	-0.20 [-1.50, 1.00]
POD 4	1.6	1.8	1.1	[0 - 3.0]	[0 - 5.5]	2.0	1.9	1.6	[0 - 3.4]	[0 - 6.3]	-0.30 [-1.50, 0.90]
POD 5	1.2	1.4	0.5	[0 - 2.5]	[0 - 4.3]	1.6	2.1	0.8	[0 - 2.6]	[0 - 6.8]	-0.40 [-1.50, 0.80]
POD 6	1.2	1.5	0.5	[0 - 1.9]	[0 - 5.3]	1.6	1.8	1.0	[0 - 3.1]	[0 - 6.0]	-0.40 [-1.50, 0.60]
POD 7	0.9	1.0	0.5	[0 - 1.8]	[0 - 2.8]	1.4	2.0	0.4	[0 - 2.3]	[0 - 7.3]	-0.50 [-1.50, 0.50]
POW 2	0.4	0.6	0	[0 - 0.6]	[0 - 2.0]	1.1	1.4	0.1	[0 - 2.1]	[0 - 4.0]	-0.70 [-1.40, 0.00]
POW 3	0.5	1.0	0	[0 - 0.8]	[0 - 3.0]	0.8	1.2	0	[0 - 1.9]	[0 - 3.5]	-0.30 [-1.00, 0.40]
POW 4	0.4	1.0	0	[0 - 0]	[0 - 4.0]	0.8	1.8	0	[0 - 1.0]	[0 - 7.0]	-0.40 [-1.30, 0.50]



B. Pain interference

	Opioid-free analgesia					Opioid analgesia					
Timepoint	Mean	SD	Median	IQR	Range	Mean	SD	Median	IQR	Range	Mean difference [95% CI]
Baseline	1.1	2.1	0	[0 - 0.7]	[0 - 7.0]	1.2	2.1	0	[0 - 2.2]	[0 - 5.9]	-0.20 [-1.50, 1.20]
POD 1	4.1	1.8	4.2	[3.2 - 5.2]	[0 - 7.1]	3.9	3.0	3.6	[1.6 - 6.5]	[0 - 8.6]	0.20 [-1.30, 1.80]
POD 2	3.0	2.2	3.4	[1.1 - 5.0]	[0 - 6.7]	3.2	2.4	3.7	[0.9 - 4.7]	[0 - 8.0]	-0.20 [-1.60, 1.30]
POD 3	2.5	2.2	2.0	[0.2 - 4.6]	[0 - 6.6]	2.7	2.5	2.7	[0.1 - 4.9]	[0 - 7.0]	-0.20 [-1.60, 1.30]
POD 4	1.8	2.3	0.6	[0 - 4.1]	[0 - 7.6]	2.1	2.4	0.9	[0 - 4.0]	[0 - 7.9]	-0.30 [-1.80, 1.20]
POD 5	1.4	2.1	0.3	[0 - 1.6]	[0 - 7.4]	1.5	2.1	0.5	[0 - 2.1]	[0 - 7.3]	-0.10 [-1.50, 1.20]
POD 6	1.2	1.8	0	[0 - 2.0]	[0 - 6.4]	1.7	2.1	0.4	[0 - 3.4]	[0 - 5.9]	-0.50 [-1.80, 0.70]
POD 7	1.5	2.4	0	[0 - 2.1]	[0 - 7.3]	1.4	2.1	0.4	[0 - 2.2]	[0 - 6.4]	0.10 [-1.30, 1.50]
POW 2	0.6	1.3	0	[0 - 0.6]	[0 - 5.3]	1.1	1.7	0.1	[0 - 1.1]	[0 - 5.6]	-0.50 [-1.50, 0.50]
POW 3	0.7	1.6	0	[0 - 0]	[0 - 5.9]	1.0	1.9	0	[0 - 0.8]	[0 - 7.0]	-0.30 [-1.40, 0.90]
POW 4	0.2	0.8	0	[0 - 0]	[0 - 3.7]	0.4	0.8	0	[0 - 0.6]	[0 - 3.1]	-0.20 [-0.70, 0.30]

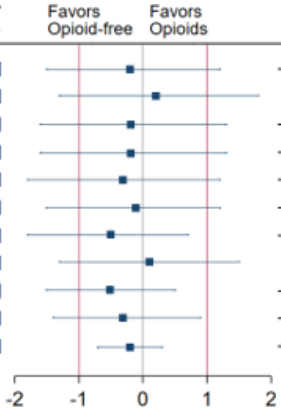
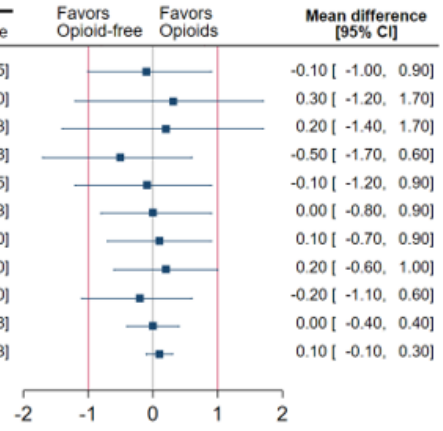


Figure A6. Subgroup analysis of Brief Pain Inventory in patients undergoing abdominal surgery.

Plots represent between-group differences in the Brief Pain Inventory severity scale (composite of 4 items, score 0-10) and interference scale (composite of 7 items, score 0-10). Red lines represent minimal clinically important differences [66,67]. POW3 OFA n = 35; POW4 OFA n = 34 (due to losses of follow-up).

A. Pain intensity

	Opioid-free analgesia					Opioid analgesia				
Timepoint	Mean	SD	Median	IQR	Range	Mean	SD	Median	IQR	Range
Baseline	0.4	1.2	0	[0 - 0]	[0 - 4.5]	0.4	1.5	0	[0 - 0]	[0 - 6.5]
POD 1	2.6	1.8	2.5	[1.8 - 4.0]	[0 - 6.5]	2.4	2.4	1.5	[0 - 3.8]	[0 - 8.0]
POD 2	2.2	2.2	2.0	[0 - 3.8]	[0 - 7.3]	2.1	2.4	1.0	[0 - 3.8]	[0 - 7.3]
POD 3	1.2	1.5	0.8	[0 - 2.3]	[0 - 4.3]	1.7	1.9	1.0	[0 - 2.8]	[0 - 5.8]
POD 4	1.2	1.5	0.8	[0 - 2.3]	[0 - 4.3]	1.3	1.6	1.0	[0 - 2.5]	[0 - 4.5]
POD 5	1.0	1.2	0.8	[0 - 2.0]	[0 - 3.5]	1.0	1.3	0	[0 - 1.8]	[0 - 4.3]
POD 6	0.9	1.3	0	[0 - 1.8]	[0 - 4.5]	0.8	1.0	0	[0 - 1.8]	[0 - 3.0]
POD 7	1.0	1.3	0	[0 - 1.8]	[0 - 4.3]	0.8	1.0	0	[0 - 1.3]	[0 - 3.0]
POW 2	0.5	1.0	0	[0 - 1.0]	[0 - 4.0]	0.8	1.4	0	[0 - 0.8]	[0 - 4.0]
POW 3	0.2	0.5	0	[0 - 0]	[0 - 1.8]	0.2	0.7	0	[0 - 0]	[0 - 2.8]
POW 4	0.1	0.3	0	[0 - 0]	[0 - 1.0]	0.1	0.3	0	[0 - 0]	[0 - 1.3]



B. Pain interference

	Opioid-free analgesia					Opioid analgesia				
Timepoint	Mean	SD	Median	IQR	Range	Mean	SD	Median	IQR	Range
Baseline	0.3	0.9	0	[0 - 0]	[0 - 3.6]	0.5	1.5	0	[0 - 0]	[0 - 6.1]
POD 1	2.3	2.0	2.0	[0.6 - 3.4]	[0 - 7.3]	2.1	3.0	0.7	[0 - 3.1]	[0 - 8.9]
POD 2	1.5	1.5	1.4	[0 - 2.6]	[0 - 4.4]	1.6	2.5	0.4	[0 - 1.7]	[0 - 7.4]
POD 3	0.9	1.1	0.3	[0 - 1.9]	[0 - 3.0]	1.5	2.5	0.1	[0 - 2.3]	[0 - 8.9]
POD 4	0.9	1.2	0.3	[0 - 1.6]	[0 - 3.7]	1.7	2.8	0.1	[0 - 2.1]	[0 - 10.0]
POD 5	0.5	0.8	0	[0 - 0.7]	[0 - 2.4]	0.8	1.7	0	[0 - 0.6]	[0 - 6.6]
POD 6	0.4	0.8	0	[0 - 0.3]	[0 - 3.1]	0.7	1.8	0	[0 - 0.4]	[0 - 7.4]
POD 7	0.4	0.8	0	[0 - 0.4]	[0 - 3.3]	0.7	1.8	0	[0 - 0.4]	[0 - 7.4]
POW 2	0.5	1.8	0	[0 - 0]	[0 - 7.6]	0.9	1.8	0	[0 - 1.4]	[0 - 5.9]
POW 3	0	0.2	0	[0 - 0]	[0 - 0.7]	0.2	0.5	0	[0 - 0]	[0 - 2.3]
POW 4	0	0	0	[0 - 0]	[0 - 0.1]	0	0	0	[0 - 0]	[0 - 0]

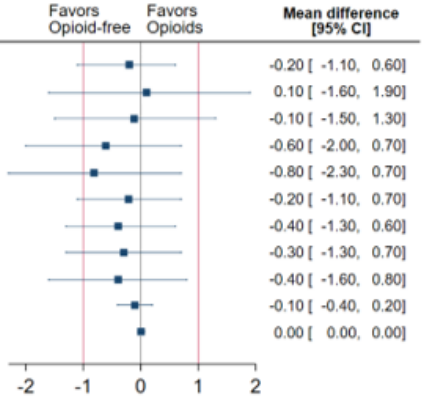


Figure A7. Subgroup analysis of Brief Pain Inventory in patients undergoing breast surgery.

Plots represent between-group differences in the Brief Pain Inventory severity scale (composite of 4 items, score 0-10) and interference scale (composite of 7 items, score 0-10). Red lines represent minimal clinically important differences[66,67]. POW3 OFA n =35; POW4 OFA n = 34 (due to losses of follow-up).

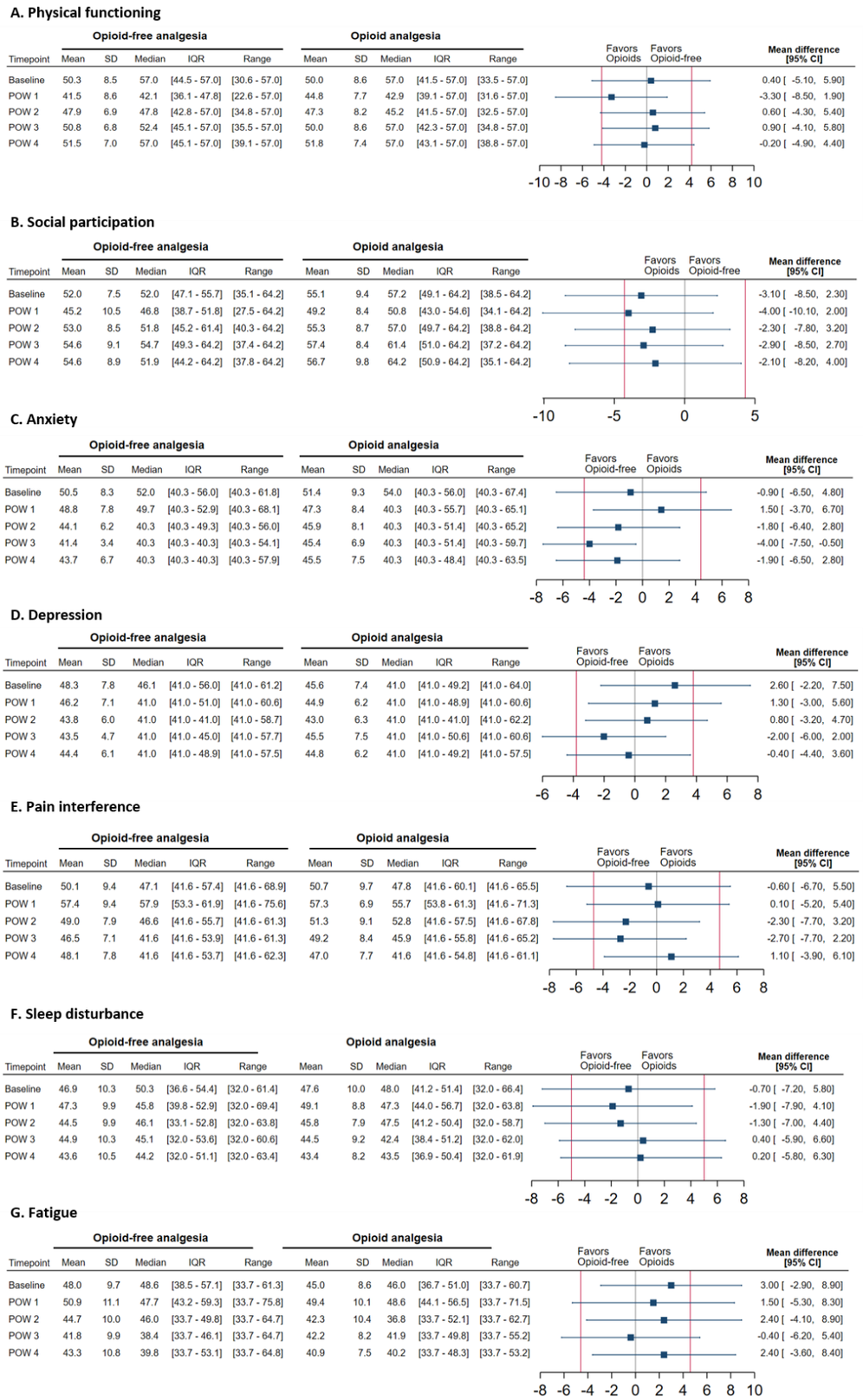


Figure A8. Subgroup analysis of PROMIS-29 domains T-scores in patients undergoing abdominal surgery.

Red lines represent minimal clinically important differences (MCID) (MCIDs were estimated as 0.5 standard deviation at baseline for each domain[65]). POW3 OFA n =35; POW4 OFA n = 34 (due to losses of follow-up). Higher scores on physical function and social participation domains indicate desirable outcomes. Higher scores on anxiety, depression, pain interference, sleep disturbance, and fatigue domains indicate undesirable outcomes. Pain intensity score is not based on the same unit of measure of the other domains (T-scores) and, therefore, is not included in the graph. Pain intensity scores are not based on the same unit of measure of the other domains (T-scores) and, therefore, they are reported separately in the table below.

PROMIS-29® pain intensity scores in patients undergoing abdominal surgery[a]

	Opioid analgesia (n=20)			Opioid-free analgesia (n=20)			Between-group difference (95%CI)[b]
	Mean (SD)	Median (IQR)	Range (max – min)	Mean (SD)	Median (IQR)	Range (max – min)	
Baseline	2.5 (2.3)	1.5 (0.5-4.5)	7 (0-7)	2.7 (2.6)	2 (0.5-4)	8 (0-8)	0.2 (-1.3 to 1.8)
Postoperative week 1	2.8 (1.7)	3 (1-4)	6 (0-6)	3.2 (1.9)	3 (1.5-4)	7 (0-7)	0.4 (-1.5 to 0.8)
Postoperative week 2	1.8 (1.8)	1 (0-3)	6 (0-6)	0.9 (0.9)	1 (0-1.5)	3 (0-3)	-0.9 (-0.1 to 1.8)
Postoperative week 3	1.1 (1.5)	0.5 (0-2)	5 (0-5)	0.8 (1.2)	0 (0-1)	4 (0-4)	-0.3 (-0.6 to 1.1)
Postoperative week 4	1.2 (1.8)	0.5 (0-1.5)	7 (0-7)	0.9 (1.2)	1 (0-1)	5 (0-5)	-0.3 (-0.8 to 1.3)

Data are mean (SD). PROMIS® = Patient-Reported Outcomes Measurement Information System. POW3 OFA n =19; POW4 OFA n = 19 (due to losses of follow-up).

[a] Pain intensity rating is a 11-point rating scale (range, 0-10; 0 = no pain and 10 = worst imaginable pain). Recall period is 7 days.

[b] Between-group difference represents mean difference.

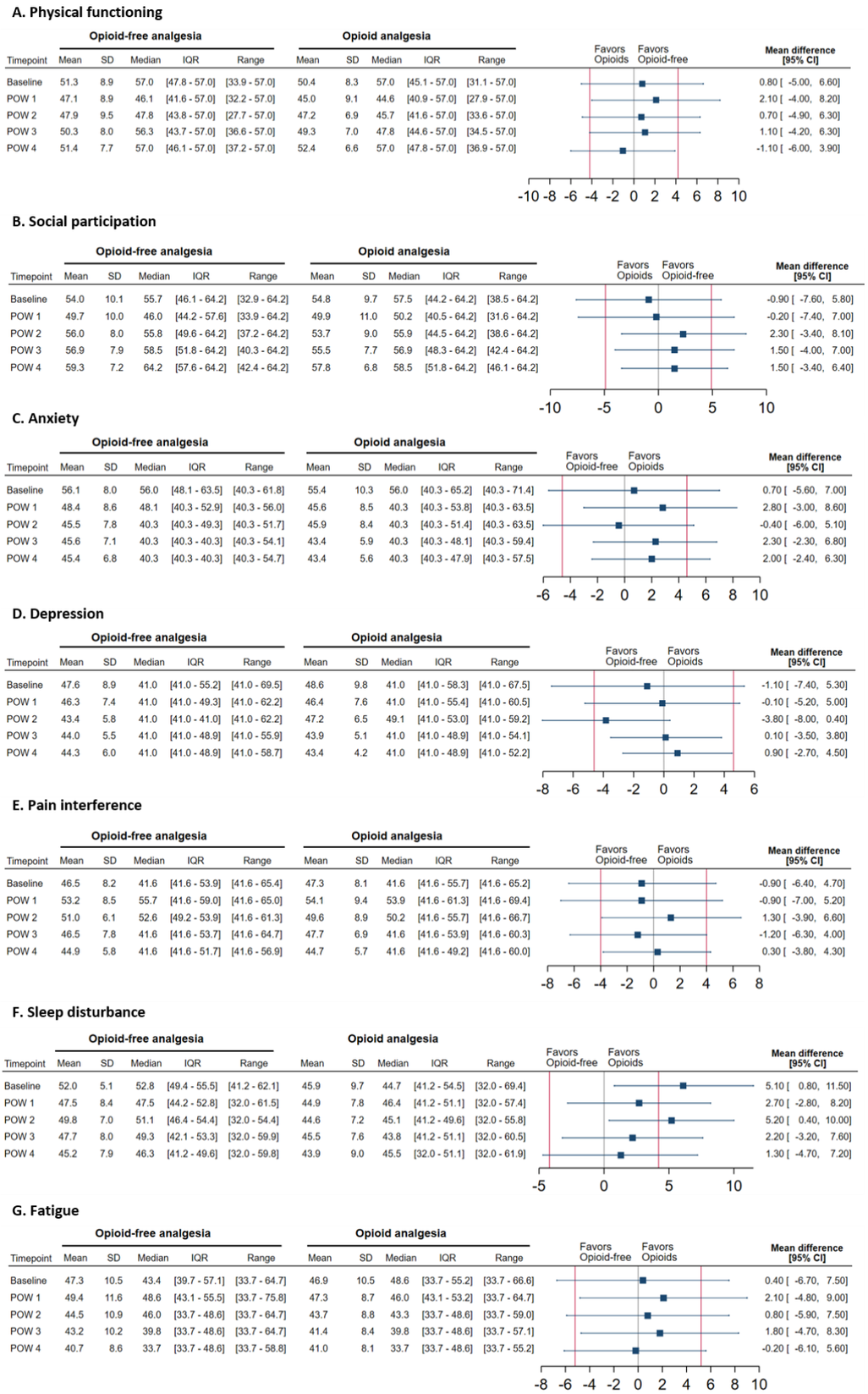


Figure A9. Subgroup analysis of PROMIS-29 domains T-scores in patients undergoing breast surgery.

Red lines represent minimal clinically important differences (MCID) (MCIDs were estimated as 0.5 standard deviation at baseline for each domain [65]). POW3 OFA n =35; POW4 OFA n = 34 (due to losses of follow-up). Higher scores on physical function and social participation domains indicate desirable outcomes. Higher scores on anxiety, depression, pain interference, sleep disturbance, and fatigue domains indicate undesirable outcomes. Pain intensity scores are not based on the same unit of measure of the other domains (T-scores) and, therefore, they are reported separately in the table below.

PROMIS-29® pain intensity scores in patients undergoing breast surgery[a]

	Opioid analgesia (n=19)			Opioid-free analgesia (n=17)			Between-group difference (95%CI)[b]
	Mean (SD)	Median (IQR)	Range (max – min)	Mean (SD)	Median (IQR)	Range (max – min)	
Baseline	1.8 (2.6)	1 (0-3)	9 (0-9)	1.6 (2.5)	0 (0-3)	7 (0-7)	-0.2 (-1.5 to 1.9)
Postoperative week 1	2.2 (2.1)	2 (1-4)	7 (0-7)	2.1 (2.2)	2 (0-3)	6 (0-6)	-0.1 (-1.4 to 1.6)
Postoperative week 2	1.3 (1.6)	1 (0-2)	6 (0-6)	1.6 (1.5)	1 (0-2)	6 (0-6)	0.4 (-1.4 to 0.7)
Postoperative week 3	0.6 (0.8)	0 (0-1)	2 (0-2)	1.2 (1.6)	1 (0-2)	6 (0-6)	0.6 (-1.5 to 0.2)
Postoperative week 4	0.3 (0.6)	0 (0-1)	2 (0-2)	0.6 (1.0)	0 (0-1)	3 (0-3)	0.3 (-0.8 to 0.3)

Data are mean (SD). PROMIS® = Patient-Reported Outcomes Measurement Information System. POW3 OFA n =15; POW4 OFA n = 15 (due to losses of follow-up).

[a] Pain intensity rating is a 11-point rating scale (range, 0-10; 0 = no pain and 10 = worst imaginable pain). Recall period is 7 days.

[b] Between-group difference represents mean difference.

Table A6. Postoperative pain management regimens

	Total	Abdominal surgery	Breast surgery
Opioid analgesia group, n	39	20	19
Acetaminophen (ATC) + Oxycodone (PRN)	19 (49)	1 (5)	18 (95)
Acetaminophen (ATC) + Naproxen (ATC) + Oxycodone (PRN)	16 (41)	16 (80)	0 (0)
Acetaminophen (ATC) + Ibuprofen (ATC) + Oxycodone (PRN)	1 (3)	1 (5)	0 (0)
Acetaminophen (ATC) + Celecoxib (ATC) + Oxycodone (PRN)	1 (3)	1 (5)	0 (0)
Acetaminophen (ATC) + Naproxen (ATC) + Hydromorphone (PRN)	1 (3)	1 (5)	0 (0)
Acetaminophen (ATC) + Hydromorphone (PRN)	1 (3)	0 (0)	1 (5)
Amount of opioid prescribed at discharge (MME)	*106 (82)*	*133 (88)*	*78 (67)*
Opioid-free analgesia group, n	37	20	17
Acetaminophen (ATC) + Celecoxib (PRN)	17 (46)	0 (0)	17 (100)
Acetaminophen (ATC) + Naproxen (ATC, switch to Ibuprofen if breakthrough pain)	17 (46)	17 (85)	0 (0)
Acetaminophen (ATC) + Celecoxib [ATC, switch to Ibuprofen or take one additional Celecoxib tablet if breakthrough pain]	3 (8)	3 (15)	0 (0)

Data are n (%) or mean (SD). MME = Morphine Milligram Equivalent; ATC = around-the-clock; PRN = *pro re nata* (as needed).

Table A7. Adverse events identified via the Perioperative Opioid-Related Symptom Distress Scale

Adverse events	Opioid analgesia (n=39)	Opioid-free analgesia (n=37)	Between-group difference (95%CI)[a]
Constipation			
7-day rate (any event)	16 (41)	12 (32)	-9 (-30.2 to 13.0)
7-day rate (clinically meaningful event)	4 (10)	2 (5)	-5 (-16.8 to 7.1)
30-day rate (any event)	18 (46)	15 (41)	-5 (-27.9 to 16.6)
30-day rate (clinically meaningful event)	7 (18)	3 (8)	-10 (-33.9 to 14.2)
Nausea			
7-day rate (any event)	8 (21)	6 (16)	-5 (-21.7 to 13.1)
7-day rate (clinically meaningful event)	1 (3)	1 (3)	0 (-7.1 to 7.3)
30-day rate (any event)	9 (23)	8 (22)	-1 (-20.2 to 17.3)
30-day rate (clinically meaningful event)	1 (3)	1 (3)	0 (-7.1 to 7.3)
Vomiting			
7-day rate (any event)	3 (8)	1 (3)	-5 (-14.9 to 4.9)
7-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)
30-day rate (any event)	6 (16)	1 (3)	-13 (-25.2 to -0.2)
30-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)
Itching			
7-day rate (any event)	13 (33)	7 (19)	-14 (-33.9 to 5.0)
7-day rate (clinically meaningful event)	1 (3)	1 (3)	0 (-7.1 to 7.3)
30-day rate (any event)	15 (38)	15 (40)	2 (-19.9 to 24.1)
30-day rate (clinically meaningful event)	1 (3)	2 (5)	2 (-6.2 to 11.8)
Fatigue			
7-day rate (any event)	31 (79)	28 (76)	-3 (-22.6 to 14.9)
7-day rate (clinically meaningful event)	2 (5)	5 (13)	8 (-4.6 to 21.4)
30-day rate (any event)	32 (82)	30 (81)	-1 (-18.4 to 16.5)
30-day rate (clinically meaningful event)	3 (8)	11 (30)	22 (-3.2 to 47.3)
Drowsiness			
7-day rate (any event)	14 (36)	13 (35)	-1 (-22.3 to 20.8)
7-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)
30-day rate (any event)	14 (36)	13 (35)	-1 (-22.3 to 20.8)
30-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)
Dizziness			
7-day rate (any event)	7 (18)	6 (16)	-2 (-18.6 to 15.2)
7-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)
30-day rate (any event)	8 (21)	7 (19)	-2 (-19.5 to 16.3)
30-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)
Inability to concentrate			
7-day rate (any event)	6 (15)	11 (30)	15 (-4.2 to 32.9)
7-day rate (clinically meaningful event)	1 (3)	2 (5)	3 (-6.0 to 11.7)
30-day rate (any event)	8 (21)	11 (30)	9 (-10.2 to 28.6)
30-day rate (clinically meaningful event)	1 (3)	2 (5)	3 (-6.0 to 11.7)
Difficulty with urination			
7-day rate (any event)	3 (8)	3 (8)	0 (-11.7 to 12.6)
7-day rate (clinically meaningful event)	1 (3)	1 (3)	0 (-7.1 to 7.3)
30-day rate (any event)	4 (10)	4 (10)	0 (-13.3 to 14.4)
30-day rate (clinically meaningful event)	1 (3)	1 (3)	0 (-7.1 to 7.3)
Confusion			
7-day rate (any event)	2 (5)	3 (8)	3 (-8.2 to 14.2)
7-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)
30-day rate (any event)	2 (5)	3 (8)	3 (-8.2 to 14.2)

30-day rate (clinically meaningful event)	0 (0)	1 (3)	3 (-2.5 to 7.9)

Data are n (%). CME = clinically meaningful event; CI = confidence interval.
A clinically meaningful event is any event with a rating of severe or very severe for all symptoms except confusion, where CME is indicated by a rating of moderate severe or very severe [40].
[a] Between-group difference indicates difference in percentages.

Table A8. Patient-reported postoperative health issues (classified using MedDRA)

Health issues[a]	Total (N = 76)	Opioid analgesia (n=39)	Opioid-free analgesia (n=37)	Between-group difference (95%CI)[b]
Headache	5 (7)	4 (10)	1 (3)	-7 (-3.8 to 18.9)
Abdominal distension	3 (4)	0 (0)	3 (8)	8 (-16.9 to 0.7)
Diarrhea	3 (4)	1 (3)	2 (5)	2 (-11.8 to 6.2)
Postoperative wound infection	2 (3)	2 (5)	0 (0)	-5 (-2.2 to 12.5)
Cough	2 (3)	1 (3)	1 (3)	0 (-7.6 to 7.3)
Urinary retention	2 (3)	1 (3)	1 (3)	0 (-7.6 to 7.3)
Hypertension	1 (1)	1 (3)	0 (0)	-3 (-2.7 to 7.8)
Tachycardia	1 (1)	1 (3)	0 (0)	-3 (-2.7 to 7.8)
Breast haematoma	1 (1)	1 (3)	0 (0)	-3 (-2.7 to 7.8)
Productive cough	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Dyspepsia	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Ecchymosis	1 (1)	1 (3)	0 (0)	-3 (-2.7 to 7.8)
Hypoesthesia	1 (1)	1 (3)	0 (0)	-3 (-2.7 to 7.8)
Neuralgia	1 (1)	1 (3)	0 (0)	-3 (-2.7 to 7.8)
Oropharyngeal pain	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Penile swelling	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Testicular swelling	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Seroma	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Urinary tract infection	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Cystitis	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)
Peripheral neuropathy	1 (1)	0 (0)	1 (3)	3 (-7.9 to 2.5)

Data are n (%).

[a] Data was obtained from spontaneous patient reporting (Patients were asked, "Did you have any significant medical problem related or unrelated to your surgery since the last study assessment?" at every postoperative time-point) and from data reported by clinicians in electronic medical records.

[b] Between-group difference represents difference in percentages.

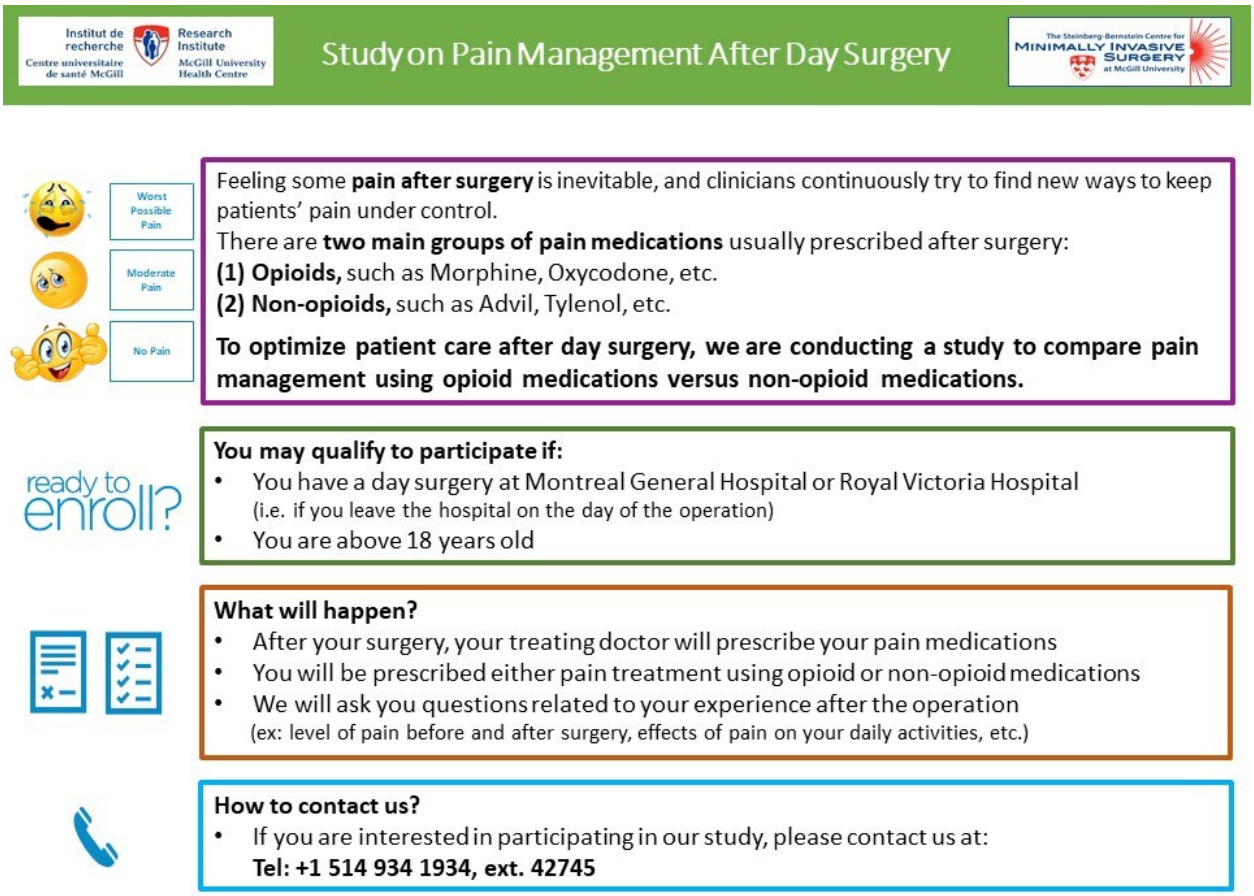


Figure A10. Study promotional poster (in English).

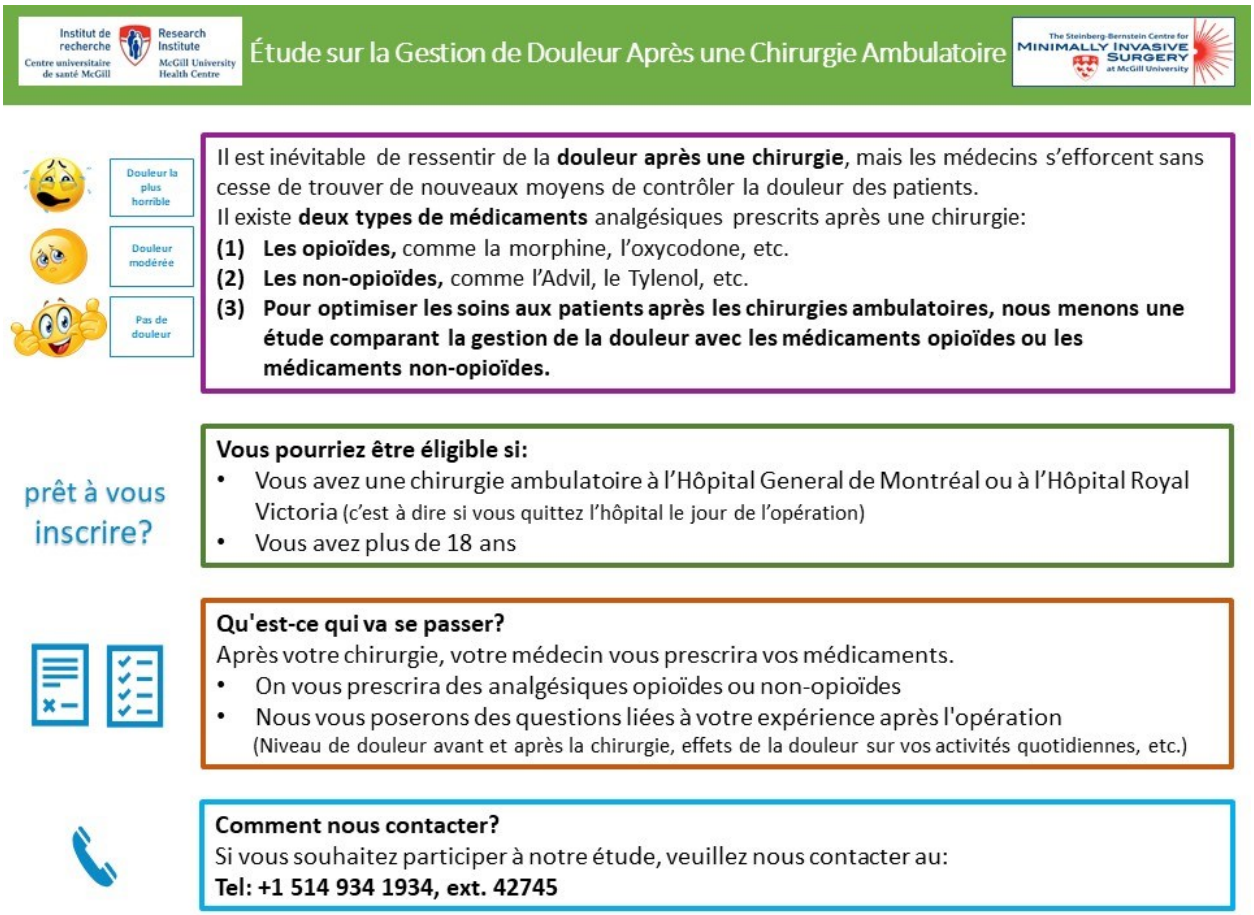


Figure A11. Study promotional poster (in French).

Table A9. COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	59
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	51
Occupation	3	What was their occupation at the time of the study?	59
Gender	4	Was the researcher male or female?	NR
Experience and training	5	What experience or training did the researcher have?	59
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	59
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	59
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	59
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	59
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	58
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	59
Sample size	12	How many participants were in the study?	60
Non-participation	13	How many people refused to participate or dropped out? Reasons?	60
Setting			

Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	59
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	No
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	Tables 3-1 & 3-2
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	58, Appendix
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	No
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	60
Field notes	20	Were field notes made during and/or after the interview or focus group?	Yes
Duration	21	What was the duration of the inter views or focus group?	60-61
Data saturation	22	Was data saturation discussed?	61
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: Analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	59
Description of the coding tree	25	Did authors provide a description of the coding tree?	Table A12
Derivation of themes	26	Were themes identified in advance or derived from the data?	59-60
Software	27	What software, if applicable, was used to manage the data?	59
Participant checking	28	Did participants provide feedback on the findings?	No
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Table 3-3
Data and findings consistent	30	Was there consistency between the data presented and the findings?	Table 3-3, Figure 3-1
Clarity of major themes	31	Were major themes clearly presented in the findings?	62-70
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	62-70

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357.

Table A10. Target sampling quotas for patients

Characteristic	Targeted quota
Age	
≤ 30 years	≥20%
≥ 65 years	≥20%
Gender	
Male	≥40%
Female	≥40%
Surgery	
Abdominal	≥20%
Breast	≥20%
Education	
Less than high school	≥20%
University degree or above	≥20%
Employment status	
Working/studying	≥30%
Retired	≥30%
Postoperative complications after hospital discharge	
Yes	≥10%
No	≥60%
Participated in the Pilot RCT	
Yes	≥70%
No	≥20%

Table A11. Target sampling quotas for clinicians

Characteristic	Targeted quota
Years of clinical experience (after residency)	
≤ 5 years	≥20%
≥ 15 years	≥20%
Practice location	
Montreal General Hospital	≥40%
Royal Victoria Hospital	≥40%
Training background	
Surgery	≥60%
Anesthesia	≥20%
Nursing	≥20%
Received formal research training (Masters, PhD)	
Yes	≥40%
No	≥20%
(For surgeons) Specialty	
General (abdominal)	≥20%
Breast Surgery	≥20%
Operated on patients involved in the trial	
≥ 3 patients	≥40%
< 3 patients	≥20%

INTERVIEW GUIDES

1. **Semi-structured interview guides for consented patients**

Acceptability of the study & personal experience with the process of recruitment

A. How were you first asked to join the study?

B. What were your initial thoughts and feelings when you first heard about the study? (Follow up: *Did you discuss your concerns and decision to participate with anyone else, how did you arrive to the final solution? Did you have any concerns when you were offered to participate? What were your concerns?*)

C. What made you want to participate? (Can you walk us through your thoughts and concerns when making a decision to participate in the study?)

D. How could we improve the way we asked you to participate in the study?

Personal experience with the process of consent

A. While in the preop clinic, a research staff gave you a consent form to sign. Can you tell us your thoughts and experience while reviewing and signing the consent form?

B. How could we improve the way we asked for your consent?

Personal experience with the research team in the PACU and the process of randomization

A. Could you tell us about your thoughts and experience interacting with the research team in the recovery room after you received your surgery? (Probes: *What was that like? How did it go? What did you think of that?*)

B. Could you tell us about your thoughts when you found out the medications you were prescribed to take home? (Probes: *Did you have preference for being assigned to one or the other medications? Why? Were you assigned to your preferred group?*)

C. Could you tell us about your experience while receiving information about how to use your medications before leaving the hospital? (Probes: *When you left the hospital, did you feel well informed about how to use your medications? Was the information clear?*)

D. How could we improve the way we inform patients about how to use their medications at home? (Probes: *Did you wish to have received more information? Do you have any suggestions on how to improve it? What would be the best way to provide information? Would written information have been useful?)*

Personal experience obtaining medications at the pharmacy

A. Could you tell us about your experience while picking up your medication at the pharmacy? (Probes: *When you left the pharmacy, did you feel well informed about how to use your medications? What did your ____ tell you about the instructions on how to take the medications?*)
B. Was the information received at the pharmacy consistent with the information received in the hospital?
C. How could we improve the way you were informed about how to use their medications at the pharmacy? (Probes: *Do you have any suggestions on how to improve it?)*

Perceived value and experiences with the intervention

A. Could you tell us about your pain experiences after your surgery when you went home, how was the first few days and weeks?
B. When, after your surgery, was your pain most intense? (Probes: *Which day after your surgery did you feel more pain? Was pain more intense during the day or at night?*) What did you take during the day?
C. Could you tell us how pain, at its worst, affected your life and daily activities? (Probes: *For example, were you able to do simple chores such as cooking and making a meal for yourself? What about other tasks?*)
D. Could you tell us how effective were the pain medications you received? (Probes: *Were the medications enough in managing your pain? Would you have benefitted from being prescribed other medications along with or instead of the ones you received?*)
E. How satisfied are you with the pain treatment you received?
F. What could have improved the way your pain was managed after the surgery?

Perceived value and experiences with the outcome assessments

A. How was your experience with responding to the surveys sent to you after your surgery? [Probes: *Did you have any difficulty accessing the surveys? How did the researchers support you in completing the surveys (if at all)?*]
B. What did you think about the survey questions? (Probes: *Did you find the questions relevant to your pain and use of pain medications? Can you remember any questions/questionnaires that you did not find relevant?*)

C. Were there any questions (if you can recall at this moment) that you did not find relevant or did not know how to answer?
D. Which question(s) asked in the survey were most relevant to your condition after the surgery? (Probes: *What is(are) the question(s) that best assessed how effective your pain treatment was?*)
E. In your opinion, what would be the ideal length and frequency of the surveys? What did you think about the length of the daily surveys? How about the weekly surveys? (Probes: *Were they too lengthy/too short?*) What did you think about the frequency in which the surveys were sent out to you? (Probes: *Were they too frequent/not frequent enough?*)
F. How did you integrate responding to the surveys in your daily routine? What was the best time of the day for you to respond the surveys and why?
G. What was your preference to receiving the survey? Via email or text message? (Probes: *Why?*)
H. What was it like having to respond our surveys daily and then weekly for 1 month? (Probe: *How satisfied you were with this approach?*)
I. Did you ever have to be reminded by our research team to respond the surveys? (Probes: *What was it like? How satisfied you were with this approach? Do you have any suggestions on how to improve it?)*
J. Overall, how could we improve in the way survey answers were collected for this study? (Probes: *Do you have any suggestions on how to improve it?)*

Closing questions

Going back to talking about the medications you were prescribed and your pain experience after the surgery…

A. What are some positive and/or negative aspects, that you can think of, while being part of this study?
B. What threats, or risks (if any) did you encounter from taking part in the study? (Probe: *Can you explain these?*)
C. With any study, we understand that there may be areas where things can be improved upon. What do you think are the main areas where we can improve in the study? (Probe: *What could we do differently? What would an ideal study look like?*)
D. Overall, how satisfied were you with the study?

E. Thinking about your overall experience with the study, how has your thoughts about pain medications and how your pain was relieved after surgery changed? (Probe: *Has your awareness of different kinds of pain medications changed since your involvement with the trial?*)

F. If you could go back, would you choose to participate again? Why?

2. Semi-structured interview guides for non-consented patients
Acceptability of the study & personal experience with the process of recruitment

A. How did you first hear about the study?

B. What were your initial thoughts and feelings when you first heard about the study? (Follow up: *Did you discuss your concerns and decision to participate with anyone else, how did you arrive to the final solution? Did you have any concerns when you were offered to participate?*)

C. If any, what were the reasons that made you not want to participate? (Probes: *Which aspects of the study made you not want to participate*? Since you mentioned that there would be time constraint in the postoperative period, we have one follow-up question for you. By participating in this study, you would be asked to fill out daily and weekly questionnaires. Did this aspect of the study influence your decision to participate in any way?)

D. Would you change anything in the way you were approached to participate in the study?

Perceived value and experiences with pain management

A. Could you tell us about your pain experiences after your surgery?

B. When, after your surgery, was your pain most intense? (Probes: *Which day after your surgery did you feel more pain? Was pain more intense during the day or at night?*)

C. Could you tell us how pain, at its worst, affected your life and daily activities? (For example, were you able to do simple chores such as cooking and making a meal for yourself? What about other tasks?)

D. Could you tell us how effective were the pain medications you received? (Probes: *Were the medications enough in managing your pain? Would you have benefitted from being prescribed other medications along with or instead of the ones you received?*)

E. How satisfied are you with the pain treatment you received?

F. What would an ideal pain treatment for your surgery be like?

Closing questions

A. Can you think of any changes to the study that would have made you want to participate? (Probes: *What do you think are the main areas where we can improve in the study? What could we do differently? What an ideal study would look like? With these changes, if you could go back, would you choose to participate?)*

B. Is there anything else you would like to add?

3. Semi-structured interview guides for clinicians

Acceptability of the study

A. How did you first hear about the trial?

B. What were your initial thoughts and feelings when you first heard about the trial?

C. Did you have any concerns when you heard about the trial?

D. What made you want to have your patients involved in the trial?

Next, I'm going to ask you specifically about your participation in the trial, such as being invited to participate, connecting with the research team, and any issues raised by patients, your team or others. We are interested in finding out about your positive and negative impressions and experiences with the trial.

Personal experience with the process of recruitment and consent

A. Please tell us your thoughts about how your patients were approached and offered to participate in the pilot trial. (Probes: *What was that like? How did it go? What did you think of that? Do you have any thoughts about how patients were approached by the research team?*)

B. Please tell us your experience if you had the opportunity to discuss the research with your patients? (Probes: *Where? How did it go? What were their reactions? Did patients demonstrate any concerns?*)

C. Would you change anything in the way patients are approached to participate in the trial? (Probe: *In the future, what would further aid our recruitment process?)*

Personal experience with the research team in the OR and the process of randomization

A. Please tell us your thoughts and experience with how randomization was conducted. (Probe: *Were you comfortable with randomizations being conducted in the OR? Were you comfortable with having a research member in the OR to conduct the randomization?*)
B. Tell us your thoughts about the timing of randomization (in the OR after the surgery). (Probe: *Was this appropriate to you? An alternative would be randomizing patients in the PACU before discharge; do you think this would work? Why or why not?)*
C. Would you change anything in the way patients are randomized in this pilot trial? (Probes: *Do you have any suggestions on how to improve it?)*

Perceived value and experiences with the intervention

A. Regarding the intervention arms, did you have preference for your patients being assigned to one or the other treatment group? Why?
B. Were you ever concerned that the medications to be received by your patient would not be enough to control their pain? Why?
C. [For breast surgeons only] Could you tell us your thoughts regarding prescribing NSAIDs to patients?
D. Currently, patients who were randomized to the non-opioid intervention have a backup opioid prescription faxed to their pharmacy. This measure is put in place so that when the patient reaches out to us regarding breakthrough pain despite use of rescue analgesics, the research team would then tell them about the backup opioid prescription. Throughout the duration of the trial, we had two patients who reached out to us. One of those patients was informed about the backup opioid prescription and the other patient was able to relieve their pain by increasing the dose of non-opioid analgesics.

   In your current practice outside of the trial, what do you recommend to patients who experience breakthrough pain?

   For the trial, could you tell us your thoughts regarding the backup opioid prescription and whether it is a necessary measure for the future full-scale RCT?

Perceived value of the outcome assessment strategy

A. After patients are discharged, are you familiar with how patients were assessed after the surgery for the study? (If not, explain to the clinician).

B. What is your impression about our outcome assessment strategy? [Probes: *Do you anticipate any issues using this assessment strategy in the future full-scale RCT?*]
C. Have you heard any feedback from patients regarding our assessment strategy?
D. In your opinion, what are valuable outcome measures to be assessed in the future full scale RCT?
E. In your opinion, what should be the primary outcome measure of the future full-scale RCT?
F. Would you change anything in the way data is collected for this study? (Probes: *Do you have any suggestions on how to improve it?)*

Experiences with patient follow up

A. During your follow-ups with patients, have patients provided any feedback regarding participation in the trial?
B. Have patients expressed any concerns about how their pain was managed after surgery?
C. Do <u>you</u> have any concerns about the pain management interventions offered to your patients?
D. Based on your experience in this study, what are your impressions about the effectiveness of opioid versus opioid-free analgesia after surgery?
E. In your opinion, what would an ideal postoperative analgesia strategy look like?

Trial design

A. What do you think are the main areas where can improve in the trial? (Probe: *What could we do differently?)*
B. What an ideal trial comparing opioid versus opioid-free analgesia after surgery would look like?

Closing questions

A. For you as a clinician, what were the main positive aspects (or benefits) of having your patients involved in this trial? (Probe: *Can you explain these?*)
B. For you as a clinician, what are other negative aspects of having your patients involved in this trial? (Probe: *Can you explain these?*)
C. For patients, what are some potential drawbacks, threats, or risks (if any) do you think exist from taking part in the trial? (Probe: *Can you explain these?*)

D. Thinking about your overall experience with the trial, how did this study affect your thoughts about pain management after surgery? (Probe: *Has your awareness of different kinds of pain medications changed since your involvement with the trial? What are your impressions about the effectiveness of opioid versus opioid-free analgesia after surgery?*)

E. If you could go back, would you choose to have your patients participating in the trial again? Why?

Table A12. Codebook

Themes	Sub-themes	Sub-subthemes	Codes
Trial engagement	Drivers to participation	Willingness to engage in research	Desiring to help get data (C3, C4, C5, C6, C7, C8, N2)
			Desiring to improve practice based on research evidence (N1, N2)
			Desiring for research progress (S3)
			Believing in research based on previous work experience (C1)
		Willingness for reducing opioid prescription	Minimizing prescribing opioids to patients postoperatively (A1, A2, S3, S4, C7)
			Aiming to train residents to prescribe less opioids (S6)
			Having concerns about opioid disposal (S2, S6, C7)
		Importance (relevance) of the study topic	Important/interesting research question (S2, A2, C2, C3, C4, C7)
			Believing relevance of research question to current overprescription (S6)
			Research usefulness toward helping patients deal with pain (N1)
			Having research interest in postop pain management (S1)
			Believes more studies on OFA effectiveness is needed (S1, S4)
			Believing necessity of investigating benefits of alternatives (S5, S6)
			Wanting to help based on prior knowledge of opioids (C3)
			Supporting research on different drugs on different people (C1)
	Drivers to non-participation	Concerns about opioid-free analgesia	Having concerns about opioid-free analgesia effectiveness (C8, NC2, NC1)
			Experiencing previous painful surgery without opioids (NC2)
			Having concerns about delay recovery if using only OFA (NC1)
			Perceiving that previous surgery was smooth because of opioids (NC2)

Themes	Sub-themes	Sub-subthemes	Codes
			Previous experiences of pain relief using opioid (NC1, NC2)
		Concerns about not having timely access to opioids	Not getting opioids is scary (NC2)
			Would participate if could request for opioids (NC1)
			Not wanting to waste time by looking for opioid-free alternatives (NC1)
Pre-trial thoughts about the interventions	Thoughts favoring opioid-free analgesia	Desire to rely less on opioids	Preference for using less medications (C8, C7, C1, C6)
			Believing in multimodal approach for managing pain (S6, A1, S1, S5, A2, S4, S2)
			Teaching patients to consistently take opioid-free analgesia around-the-clock (N2)
			Relying less on opioids as first course analgesics (N2)
			Declining opioid use by teaching patients not to use it first course (N1)
			Declining opioid use by teaching patients to use half or quarter dose (N1)
			Increasing opioid-free analgesia effectiveness by giving it before pain starts (N1)
			Noticing trend in decreasing opioids being prescribed and used (N2)
			Reducing amount of opioids on standardized prescriptions (S5)
			Believing opioid-free analgesia for ambulatory surgical patients is adequate for pain (S3)
			Having pain issues less common with breast surgeries (S3)
			Believing it's uncommon for ambulatory patients requiring more than small doses opioids (S5)
			Few exceptions where patients require more opioid pills (S5)
			Believing patients stop taking opioids after first few days (S5)
			Believing opioids are overprescribed (S2, S6)
			Having interest in research for minimizing medications after surgery (C7)
			Believes opioid is not needed for low pain surgeries (C3)
			Believing surgery patient is going to undergo is common and shouldn't cause much pain (C6)
			Believes that opioids were not needed for this surgery (C6)
			Believing opioid-free analgesia is a sufficient alternative for pain control (C3)
			Believes lots of pain meds are prescribed after surgery (C7)
			Preferring patients randomized to opioid-free analgesia (S2)
			Prioritizing opioid-free analgesia over opioid analgesia (N1)

Themes	Sub-themes	Sub-subthemes	Codes
			Not giving opioids is fantastic (S2)
			Believing that all surgeons should not prescribe narcotics (S6)
			Planning to change from prescribing opioids (S1)
			Thinking to consider opioid-free analgesia as another option (N1)
			Believing existence of other alternatives to manage pain (N1, A2)
			Providing patient comfort and preventing pain through education (N1, N2)
			Not liking opioids (C1, C3, C5)
			Preferring to prescribe narcotics only during immediate postop (S6)
			Wanting to provide comfort with minimal opioids (N1)
			Perceiving opioid prescription as a negative (C3)
		Concerns about safety of opioids	Having concern about addiction (C1, C3, C5, S6, C8)
			Having concerns with opioids (C3)
			Concerned of taking opioids (C3)
			Fear of taking opioids due to opioid crisis (C3)
			Husband having concern about addiction with study participation (C2)
			Having negative reaction to opioids due to media representation (C1)
			Having addiction concerns eased by researchers (C8)
			Minimizing opioid use because of potential misuse and addiction (S4)
			Being concerned with side effects of opioids (S2)
		Believing opioids may mask symptoms of serious complications	Persistent pain indicating postoperative complications (S2, S6)
			Attributing prolonged pain to surgical complications (S2, S6)
	Thoughts favoring opioid analgesia	Concerns that opioid-free analgesia may be less effective	Difficult transitioning toward opioid-free analgesia by considering surgery characteristics (S1, S6)
			Having concerns that patients will experience pain (N2, S5)
			Concerning about patient's comfort at home due to opioid-free analgesia (N1)
			Feeling nervous when informed of opioid-free analgesia (C8)
			Feeling scared about inadequate pain relief from OFA (C8)
			Having concerns about opioid-free analgesia effectiveness (A1, C8, NC2)
			Fear of discharging patients without routine meds and opioids (N1)

Themes	Sub-themes	Sub-subthemes	Codes
		Believing may benefit patients with breakthrough pain	Believing there's minimal benefits to eliminating opioids (S5)
			Giving opioids for breakthrough pain (S4, S5, S6)
			Risking patient in pain if opioids is not readily available (S2, A2)
			Using opioids as needed before pain became intense (NC2)
			Feeling more comfortable if patients have backup opioids (N1)
			Believes patients only fill out backup opioids if needed (S4)
			Giving opioids as needed depending on reported pain level (N1)
		Concerns about undermanaged acute pain evolving into chronic pain	Not treated acute pain turns into persistent postoperative pain (A2, S4, S3, A2)
			Treating persistent surgical pain tougher than acute pain (A2)
		Concerns about side effects of opioid-free analgesia	Having concerns about risk of bleeding from NSAIDs use (S3, S5)
			Having renal complication as an endpoint in full-scale trial (A1)
			Having concerns about renal complications with multiple NSAIDs use (A1)
			Concerning about side effects from NSAIDs (S5)
			Finding appropriate analgesia for patient who can’t take NSAIDs (S5)
			Ensuring minimal complications with NSAIDs (S3)
Postoperative pain experiences	Experienced minimal pain	Experiencing low levels of pain	Not needing many medications because of high pain tolerance (C7)
			Preferring Celebrex for the next surgery (C1)
			Experiencing some inflammation at surgical site (C4)
			Feeling burning sensation at surgical site (C3)
			Having a bruise/ache postop (C1, C5)
			Not having much/horrendous postop pain (C1, C7, C4, C5, NC2)
			Not feeling actual pain postop (C3)
			Managing pain with non-opioids only (C1, C7, C3)
			Experiencing low (minimal) pain (C3, C4, C7, NC2)
		Daily activities not affected by pain	Able to perform simple chores (C1, C5, C7, NC2)
			Sleeping not affected by pain (C1, C4, C3, NC2)
			Managing pain without help (C2)
	Experienced considerable pain	Experiencing moderate yet manageable pain	Experiencing considerable pain first two days postop (NC1)
			Experiencing more pain at night (C8, C2, NC1)
			Experiencing more pain during the day (C3, C4)

Themes	Sub-themes	Sub-subthemes	Codes
			Experiencing bearable pain with medications (NC1, C2)
			Experiencing pain equivalent to C-section (C8)
			Experiencing pain from postoperative complications (C7)
			Experiencing that worst pain was still manageable
			Analgesics not being 100% effective but kept pain manageable (C6)
			Keeping pain manageable by taking non-opioids (C3, C1, C4, C7, NC1)
			Experiencing considerable pain that needed opioids (C2)
			Experiencing some pain that did not need opioids (C3, C4)
		Experiencing intense pain	Experiencing momentary intense pain during sudden movements (NC2)
			Needing additional analgesics in PACU (NC1, C8)
			Experiencing extreme pain in immediate postoperative period (C2, C8)
			Experiencing most intense pain postoperative day 2 (C3, C4)
			Experiencing worst pain immediately after waking up from surgery (C2)
			Severe intermittent pain from gas injected into abdomen (NC2)
			Extreme pain quickly managed and under control in PACU (C2)
			Experiencing intense, swelling pain; called hospital for help (C6)
		Pain resolved within one week	Able to move around as pain resolved (C4, C8, NC1)
			Pain progression resolved within a few days (C4)
			Not needing to take pain medications after 1 week postop (C7)
			Resuming regular activity one week postop (C2)
			Experiencing pain that did not fluctuate much after first week (C4)
		Quality of life was affected by pain	Minimizing movements to avoid pain (NC1, NC2)
			Pain affected quality of life quite a bit (C6, C8, NC2)
			Experiencing some difficulty moving around first few days (C4, C8)
			Not able to perform simple chores first week postop (C3)
			Having some difficulty laying flat down (C1)
			Requiring help for moving around because of pain (C8)
			Pain affecting sleep quality (C8, NC1)

Themes	Sub-themes	Sub-subthemes	Codes
Trial acceptability	Positive experience with participation	Patients receiving more care in trials	Feeling cared for with questionnaire follow-ups (C2)
			Having more awareness of recovery process (C3, C4)
			Being reassured with many and long follow-ups (N1)
			Enrolling patient in research exposes them to more care (N2, S5, S1)
			Patients doing better clinically from participating in trials (S5)
			Providing more benefits for patients related to closely following up (N1)
		Increased awareness and acceptance of different pain management options	Having more awareness of medications use and how it affects patient (C6, C8)
			Having more awareness of pain and appropriate analgesics (C4)
			Being more comfortable with opioid-free analgesia after participation in the trial (A1, S2)
		Satisfaction with trial	Being very satisfied with trial participation (C2, C5, C8, C1, C7, C6)
			Satisfied with the received intervention (opioid-free analgesia) (C1, C5, C8)
			Satisfied with the received intervention (opioid analgesia) (C2, C4, C6)
			Satisfied with assigned group (C3, C7, C4)
			Satisfied with treatment and dealing with pain (C3, C4, C5, C6)
			Perceiving that study was easy to participate (N2, C7)
			Everything proceeds well and better than expectation (C3)
			Patients expressing to surgeon they were pleased with study (S6)
			Perceiving that patient is comfortable with trial (N1)
			Friendly and helpful approach of researchers to participants (C5, C8, C1)
			Experiencing positive interactions with researchers (C7, C4)
			Appreciating availability of researchers (C1, C8, N1, N2)
			Perceiving that trial is safe (N2)
		Lack of drawbacks	Experiencing no drawbacks from trial participation (C1, C2, C3, C4, C5, C6, C7, C8, S4, S6)
			Having no concerns about trial conduct (C6, S1, S2, S3, S4, A1, N1, N2, S5, S6)
			Mitigating issues to make trial easier to participate in (S5)
			Perceiving minimal burden from trial participation (C7, C8)
			Seeing no negative aspects with pilot trial (N2, S5, S6)

Themes	Sub-themes	Sub-subthemes	Codes
			Having no concerns about trial interventions (S1, S2)
			Not needing any improvement/changes to trial conduct (C2)
			Having no concerns of the prescribed medications (C5)
			Not being concerned about types of pain meds (C4)
			Well-constructed trial with no problem for patients (S6)
	Coherent interventions	Adequate protocol for delivering the interventions	Receiving comprehensive explanation of discharge prescription (C1, C7, C4, C5)
			No necessity to change how patients are instructed to take medications (C4, C5, C8)
			Double-whammy instructions regarding taking prescribed meds (C2, C3, C4, C5, C7, C8)
			Having no difficulty integrating trial interventions in routine patient care (S1, S3, S6)
			Feeling comfortable teaching prescribed medications (N1, N2)
			Getting comforting explanations about discharge follow-up (N1, N2)
			Remembering easily because of comprehensive explanation (C1)
			Clarified patient questions about medications (C1)
			Reassuring explanation about pain and its control (C2)
			Receiving comprehensive instructions (C4)
			Receiving written instructions (C5)
			Comprehensive instructions regarding taking meds (C3)
			Receiving clear and transparent drug info in each group (C4)
			Appreciating having different types and lots of prescribed meds (C6)
			Appreciating written instructions because difficult to remember (C8)
			Enrolment did not affect anesthesia plan (A2)
			Treating patient following routine care protocol (N1)
			No changes in routines regarding educating prescribed meds (N1)
			Receiving clear and transparent drug info in each group (C4)
		Reassured by backup opioids	Comforting to have backup opioid prescription (S3, S4, S5, S6)
			Reassuring results related to a small number of opioid backup (S6)
			Appreciating option to give opioids if pain is not well-controlled (S5)
			Backup opioids unnecessary for future trial (S2)

Themes	Sub-themes	Sub-subthemes	Codes
	Appropriate data collection process	Suitability of questionnaires	Perceiving questions as relevant (C1, C3, C4, C5, C6, C7, C8)
			Appropriate frequency of questionnaires being sent out (C8, C6, C2, C7, C4, C3)
			Preferring to receive questionnaires by email to fill at leisure (C3, C1, C7, C2, C6, C4)
			Responding to questionnaire fit into daily routine (C7, C1, C3, C6)
			Perceiving questionnaires as clear and easy to answer (C1, C4, C6, C3)
			Appropriate length of the questionnaires (C1, C3, C2, C4, C6)
			Appreciating pain severity question as most relevant (C6, C4, C2)
			Satisfied with the way data is collected for the study (C4, C6, C5)
			Appreciating thorough physical and mental questions (C3, C2)
			Having a flexible schedule to respond to questionnaires (C5)
			Responding to survey was brief (C4)
			Satisfied with responding to questionnaires over the phone (C5)
			Satisfied with questionnaires (C4)
			Experiencing no difficulty with accessing the questionnaires (C4)
			Answering questionnaires was not time-consuming (C7)
			Being satisfied with outcome assessment strategy (N1, N2, S1, S2, S3, S4, S5, S6, A1)
			No need to change outcome assessment strategy (S2, S4, S1)
			Outcome assessment strategy common across studies (A2)
		Helpfulness of questionnaire reminders	Filling out emailed surveys following twice reminders (C6, C3)
			Filling out survey after two email reminders (C2)
			Feeling embarrassed and thankful for survey reminder (C2)
			Perceiving reminders as helpful (C4)
			No need to change the way patients are reminded about survey (C6)
			Appreciating reminder to fill out questionnaires (C8)
			Missing deadline due to drowsiness (C8)
	Sound research methods	Appropriate consent process	No concerns regarding consent process (C7, C4, C5, C1, C8, C2, C6)
			No necessity to change obtaining consent (C7, C2, C1, C6, C5, C4)
			Transparency of obtaining informed consent: clear and informative (C3, C4)
			Not feeling pressured to participate (C4, C3)

Themes	Sub-themes	Sub-subthemes	Codes
			Appreciating consent in person (C8)
			Having no hesitancy in participating and signing consent form (C5)
			Calling for consent was appropriate (C3)
			Previous education helped understanding informed consent form (C3)
			Feeling good about the process of obtaining informed consent (C3)
		Appropriate recruitment process	Appropriateness of invitation process to participate in trial (C3, C6, C7, C8, C2)
			Being satisfied with recruitment strategy (S1, S2, S3, S6)
			No need to change recruitment strategy (S1)
			Relying on research team to approach and recruit patients (S1)
			Recruiting appropriate patients (S5)
			Appropriateness of selected population (S6)
			Collaborating with surgeon in attracting patients to participate in study (S6)
		Appropriate randomization process	Randomizing in operating room (OR) was appropriate (A1, A2, S1, S2, S3, S4, S5, S6)
			Being comfortable with having researcher in OR for randomization (S1, S2, S6)
			Difficult finding staff to sign prescription if randomizing in PACU (S3, S5, S2)
			No need to change randomization strategy (S1, S5)
			Preferring randomization in OR (A2)
			Preferring not having to sign 2 prescriptions if one goes unused (S5)
			Requiring OR staff to sign 2 prescriptions if randomize in PACU (S5)
			No issues with signing pre-written prescription (S4)
Trial refinement for full-scale RCT	Optimizing postoperative pain management interventions	Individual conditions may impact pain management	Finding that NSAIDs were insufficient for first few days postop (C8)
			Using self-convincing strategy to accept treatment allocation (C8)
			Concerning about prescribed dosage of opioid-free analgesia for surgical pain (C8)
			Not experiencing much pain after undergoing many surgeries (C7)
			Desiring for individualized prescribing (C6)
			Believes different people needs different amount of pain medications (C7)
			Revising analgesia strategy if pain not controlled early on (A2)
			Needing additional opioids for pain control (C2)
			Considering patient and surgical factors for anesthesia plan (A2)
			Considering patient- and surgical-related factors for peripheral nerve blocks (PNBs) (A1)

Themes	Sub-themes	Sub-subthemes	Codes
			Requiring different pain treatments for different surgeries (A2)
			Against standardizing intraoperative anesthesia plan for every patient (A2)
			Patient and surgical factors influencing level of postop pain (N2)
			Changing analgesia strategy could be difficult from RCT point-of-view (A2)
		Setting patients' expectations	Teaching patient to take opioid-free analgesia around-the-clock before using opioids (A1)
			Teaching patients that pain is normal and expected after surgery (S4, A2, S2, S6)
			Better managing pain instead of eliminating it (S6)
			Reassuring patient that postop pain is going to be short lasting (N2)
			Believing pain is normal part of surgery (C3)
			Managing stress and control to improve pain tolerance (C3)
		Emphasizing non-pharmacological strategies to relieve pain	Massaging surgical site to relieve pain (C7, C1)
			Preferring to use non-medicinal strategies to cope with pain (C7)
			Suggesting teaching patient massage techniques & exercises (C7)
			Believing non-medicinal strategies helps reduce meds side effects (C7)
	Potential sources of bias	Additional analgesics in PACU could influence pain outcomes	Experiencing manageable pain first postop day due to PACU medications (C6, C1)
			Additional analgesia given in PACU due to late discharge (C1)
			Being aware of allocation could influence immediate postop care (A1)
		Inconsistency of intraoperative regimens	Technical differences among anesthesiologists in doing a PNB (A1)
			Availability of PNBs has potential to reduce opioid use (N2)
			Considering preoperative analgesia in analyzing process (A1)
			Considering adjunct analgesics used intraoperatively (A1)
			Giving more analgesia intraoperatively if knowing patient will not have opioids postop (A2)
			Knowing that patient received PNBs changes readiness to give opioids (N2)
		Information given by pharmacies vary	Receiving more explanations by pharmacist (C6, C2)
			Comprehensive explanation from pharmacy (C3)
	Optimizing patient screening and randomization	More stringent screening process	Double-screening high-risk patients during recruitment (A1)
			Being opioid-dependent a risk for trial participation (S4)

Themes	Sub-themes	Sub-subthemes	Codes
			Identifying patients at risk for having problems with pain (S5)
		Considering bias in current randomization strategy	Suggesting randomizing prior to surgery (S4)
			Randomizing preoperatively may help set patient expectations (S4)
			Randomizing in OR could introduce bias (A1)
			Suggesting randomizing in PACU to prevent bias in anesthesia (A2)
			Stratifying randomization based on presence of peripheral nerve blocks (A1)
	Decreasing participant burden	Difficulties with responding to questionnaires	Having difficulty responding to questionnaires few days postop (C7, C8)
			Having more difficulty recalling with weekly questionnaire (C3)
			Having difficulty answering some questions (C7)
			Challenging to answer questions because feeling "very normal" (C3)
			Finding questions irrelevant as patient recovered (C8, C7)
			Confusing survey question about taking prescribed medications (C2)
			Perceiving pain severity challenging to answer (C3)
			Perceiving pain severity questions as irrelevant (C1)
			Perceiving ambiguity in questions (C7, C6)
			Finding questions about mental health tough to answer (C6)
			Finding that some questions were unspecific and irrelevant (C7)
			Perceiving questions as important despite them not being personally relevant (C3)
			Feeling annoyed and rushed about reminder while experiencing postoperative complication (C7)
		Reducing length and frequency of questionnaires	Having follow-up once a week to decrease participant burden (S5)
			Willing to participate in shorter studies (C6)
			Finding that questions were repetitive (C7, C6)
			Finding that follow-ups were too frequent because not much change (C7)
			Suggesting removing repetitive questions (C7)
			Finding that length of questionnaires too long (C7)
			Regretting about participation (C6)
			Suggesting that length of questionnaire varies for different patients (C8)
			Believes that study duration should match recovery duration (C6)
		Having concerns with increased workload	Being concerned with increased workload from trial participation (S3)

Themes	Sub-themes	Sub-subthemes	Codes
			Believes patients may be overwhelmed by participating in research (S1)
			Expecting discomfort due to study participation (C3)
			Having concerns about time commitment for survey completion (NC1)
	Optimizing outcome assessment	Assessing pain outcomes	Assessing pain control as primary outcome (S3, S5, S1, S4)
			Assessing pain once a month in last three months (A2)
			Assessing need for backup opioids as secondary outcome (S1)
			Extending pain assessment to at least 6 months (A2)
			Assessing pain control as secondary outcome (S2)
			Assessing need for backup opioids as primary outcome (S2)
			Assessing pain, side effects, and need for opioids (S5)
			Having primary outcome be continuous and measured on VAS (S5)
			Doing sensitivity analysis to determine difference in pain (A2)
			Difficulties in assessing request for backup opioids (S2, S5, S6)
			Wanting to know percentage patient who needed opioids but did not get it (S1)
			Suggesting that questions be more specific to surgery pain (C6)
		Assessing physical and mental health functions	Assessing physical and mental function with respect to pain (N2, A2)
			Considering coping strategies with pain as one of outcomes (N1)
			Finding questions about mental health tough to answer (C6)
			Finding questions about mental health irrelevant, mood wasn't affected (C8)
		Assessing side effects related to interventions	Assessing side effects from NSAIDs as secondary outcome (S2)
			Assessing side effects of opioids vs opioid-free analgesia (S5)
			Assessing adverse events to ensure safety in main trial (A1)
		Administering questionnaires via email and text messages	Combining email and phone call strategies for outcome assessment (S4, S6)
			Preferring to receive survey via both email and text (C8)
			Potential to miss surveys when sent via email (C8)
			Lacking reliable methods for patients to contact treating team (S2, N2, A2, S5)

Themes	Sub-themes	Sub-subthemes	Codes
	Ameliorating communication strategy	Enhancing communication with patients	Difficult remembering interaction with researcher in PACU (C3, C1, C8)
			Preferring to have written instructions on how to take medications (C3, C8)
			Receiving too many medications was confusing (C6)
			Feeling overwhelmed with many types of meds on prescription (C6)
			Difficulty accessing more pain medications on weekend (C2)
			Difficult for patients accessing personal counseling for pain (A2)
			Suggesting tracking medication intake with a table/diary (C6)
			Having a box for patients to report/explain instead of just rating (A2)
			Difficulty understanding due to anesthesia (C8)
			Having difficulty getting in contact with researchers (C3)
			Receiving inadequate info on how to take medications (C6)
			Would appreciate more information on pain, recovery, appropriate meds (C6)
			Would appreciate a more thorough explanation of medications (C6)
			Would feel safer knowing about backup measures in place (C8)
			Getting impression of receiving no painkillers (NC2)
			Wanting to know about effectiveness of both groups (NC1)
			Wanting to know more about alternatives to opioids (NC2)
			Believes that others may need more or less instructions on how to take medications (C7)
			Having hesitancy to call hotline because didn't want to ruin data collection (C8)
		Enhancing communication with clinicians	Developing a coherent opioid-free analgesia approach involving anesthesia (S1, A1)
			Involving anesthesia in planning of future full-scale RCT (S1)
			Letting surgeon and anesthesiologist work pragmatically (A2)
			Difficult to verbally reach every involved personnel (N1)
			Informing staff to be more coherent and coordinated (N1)
			Finding out about study after enrollment of first patient (N1)
			Distributing written materials for staff to read on their own (N1)
			Feeling ill-prepared initially because unfamiliar with trial (N1)

Themes	Sub-themes	Sub-subthemes	Codes
			Ensuring thorough communication with OR before randomization (A1)
			Providing more information to PACU nurses prior to trial start (N1)
			Having trial posters in nurses' lounge (N1)
			Being unsure of whether to give something more to patients in opioid-free analgesia group (N1)
			Having problems getting more pain medications in PACU (C8)

C = consenting patient; NC = non-consenting patient; S = surgeon; A = anesthesiologist; N = nurse

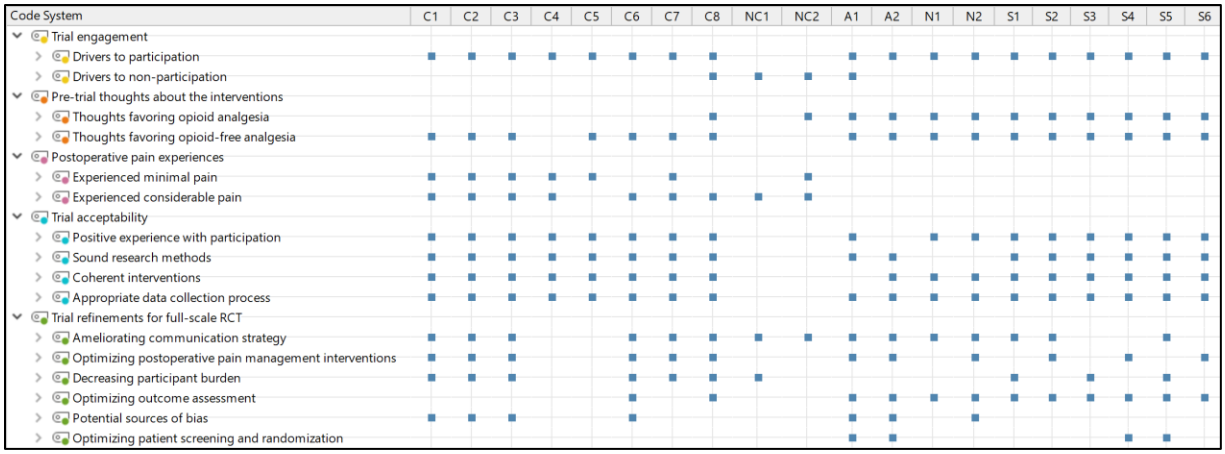


Figure A12. Saturation grid

C = consenting patient; NC = non-consenting patient; S = surgeon; A = anesthesiologist; N = nurse

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INFORMATION AND CONSENT FORM

(PILOT RCT)

Research Study Title:	**Opioid-free analgesia after outpatient surgery: A pilot randomized controlled trial**
Protocol number:	2020-5965
Researcher responsible for the research study:	Julio Fiore [1,2]
Co-Investigator(s)/sites:	Liane S. Feldman[1,2], Gabriele Baldini, MD [3]

1. Division of General Surgery, McGill University Health Center, Montreal, Canada
2. Steinberg-Bernstein Center for Minimally Invasive Surgery, McGill University Health Centre, Montreal, Canada
3. Department of Anesthesiology, McGill University Health Center, Montreal, Canada

INTRODUCTION

We are inviting you to take part in this research study because you will have a surgery in our hospital. However, before you accept to take part in this study and sign this information and consent form, please take the time to read, understand and carefully examine the following information. You may also want to discuss this study with your family doctor, a family member or a close friend.

This form may contain words that you do not understand. We invite you to speak to your doctor or to a member of the research team, and ask them to explain to you any word or information that is unclear to you before you sign this form.

BACKGROUND

Feeling some pain after surgery is inevitable, and doctors continuously try to find new treatments to keep patients' pain under control. Pain medications (analgesics) are drugs used

to relief pain after surgery. Because the pain process is complex, there are many varieties of medications that provide pain relief. Pain medications are usually divided into two main groups: opioids and nonopioids. Opioids are drugs that contain chemicals that help relaxing the body and relieving pain. Their use require prescription by a doctor. Non-opioid drugs contain chemicals that relive pain in different ways (for example, by reducing inflammation) and they can be either prescribed by a doctor or purchased over-the-counter in your pharmacy (for example, Tylenol, Advil, Aleve, etc.). In several countries across the world, pain medications prescribed after surgery commonly include only non-opioid drugs. In Canada and in the United States, doctors often prescribe opioid drugs in addition to non-opioid drugs. At the moment, the best drug treatment to relief pain after surgery is unknown.

PURPOSE OF RESEARCH STUDY

The goal of the proposed pilot study is to evaluate recovery after surgery when patients (1) receive treatment for pain using only non-opioid medications and (2) receive treatment for pain including the prescription of opioid medications.

DESCRIPTION OF THE RESEARCH PROCEDURES

This research study will take place at McGill University Health Centre (Montreal General Hospital and Royal Victoria Hospital). For this research study, we plan to recruit about 80 participants, men and women over the age of 18.

All the patients who have a surgery will receive a prescription of pain medications before they leave the hospital. If you agree to participate in the study, you will be randomly assigned (similar to a flip of a coin) to one of the two groups after your operation.

- If you are in Group 1: you will receive a prescription of opioid-free medications to relief pain after your operation.
- If you are in Group 2: you will receive a prescription of opioid-free medications and also opioid drugs to relief pain after your operation.

Prescriptions will only include pain medications that are currently in use and approved in our hospitals. **The dose and frequency of the medications will be decided by your treating doctors based on your individual needs**.

All relevant information related to your recovery after surgery, for example, where to obtain your pain medications, how much and/or how often to take them, what to do in case your pain becomes stronger than expected, will be provided by a hospital nurse before you leave the hospital. All patients having a surgery at our hospitals receive information about what they can to do and what to expect after a surgery. This is a part of the standard care in our hospitals.

Before Surgery

Before surgery we will ask you to complete questionnaires about your overall health, whether you feel pain and how pain affects your life. We will also ask about your current work status, if you take medications for pain and what type(s) of medications you take, and your expectations about the effect of different pain medications. The completion of these questionnaires will take about 15-20 minutes.

After Surgery

During the first 7 days after the surgery, once a day, preferably in the morning, we will ask you to complete questionnaires about pain and how pain affects you daily life, for example, whether pain affects your ability do your daily activities and concentrate, etc. These questionnaires will also ask whether you took the pain medications prescribed by your doctor. These questions are necessary because it is known that some people may use all prescribed medications, others may use half of them and/or some may have changed medication(s). The completion of these questionnaires will take about 5-10 minutes.

At the end of week 1,2,3, and 4, in addition to the pain-related questions, we will ask you whether you have problems doing your normal daily activities (i.e., vacuuming, shopping, etc.), how good your sleep was, how much fatigue you felt, etc. The completion of these questionnaires will take about 15-20 minutes.

We may either send you a link to your email to respond to the questions electronically or we may call you so you can give your responses over the phone. The choice will be up to you. Please note that, if you prefer to complete the questionnaires on the phone, you will receive two phone calls (one to respond about your medications use, and one to respond the remaining questions).

RISKS OR INCONVENIENCES ASSOCIATED WITH THE STUDY

The study interventions involve medications that are commonly used in our hospitals. Potential risks associated with their use are well known. Possible reactions to opioid pain medications include sleepiness, constipation, nausea, itching, allergic reactions, problems with thinking clearly, slowing of reactions and risk of addiction. Possible reactions to non-opioid pain medications include stomach pain and heartburn, risk of increased bleeding, allergic reactions, liver and kidney problems. As with any study assessing medications to manage pain, we cannot exclude that the medications received by one groups will be more (or less) effective than the medications received by the other group.

As per hospital standard care, before your discharge from the hospital, a surgery nurse will meet with you to explain how to best prevent these potential risks and what to do if you experience any problems. Information on how to avoid risks of pain medications are also often given by pharmacists when your medication is dispensed. In addition, before you leave the hospital, you will receive a sheet with information on how to proceed in case you have issues with your pain treatment.

Your treating doctors will be aware of your participation in this study and they will prescribe all pain medications given to you. Your doctor and members of the research team will answer any questions that you may have regarding the risks, discomforts and side effect associated with the medications used in this study. **Your surgeon may change your medications or put an end to your participation in the study at any time if he/she considers that to be of your best interest.**

Your personal information will be stored in a secure server and in a way that complies with all privacy law in Canada. This information will not be sold or provided to any third-party under any circumstances. However, whenever information is transmitted over a wireless network, there is always a possibility that privacy could be breeched.

BENEFITS ASSOCIATED WITH THE STUDY

You may or may not personally benefit from your participation in this research project. We also hope that the study results will contribute to the advancement of scientific knowledge in this field and help us find better treatments for surgical patients.

OTHER POSSIBLE TREATMENTS

You do not have to take part in this study to receive medical care for your condition. Your access to standard medical information and your treating doctors will be in accordance with our usual practices.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from the project at any time, without giving any reason, by informing the study doctor or a member of the research team.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the study doctor or clinical team.

Your treating doctors, the study doctor, the Research Ethics Board, the funding agency, or the Sponsor may put an end to your participation without your consent. This may happen if new findings or information indicate that participation is no longer in your interest, if you do not follow study instructions, or if there are administrative reasons to terminate the project.

Any information collected up to the time you withdraw from the study will be stored and may continue to be used in order to maintain the integrity of study data. Please inform the study personnel if you want the data collected up to your withdrawal to be retracted and destroyed. However, any analyses already completed using that data will be kept.

CONFIDENTIALITY

The researchers will only collect information required to meet the scientific goals of the study. The study file may include information from your medical chart, including information concerning your past and present state of health, your lifestyle, as well as the results of the tests, exams, and procedures that you will undergo during this research project. Your research file could also contain other information, such as your name, sex, date of birth and ethnic origin. To protect your privacy, your information will be identified with numbers and or letters. Only the investigator in charge of the study knows the numbers and/or letters that link them to you. This information will be kept as a separate list kept by the investigator in charge of the study. All the information collected about you during the study will remain confidential as the law requires.

Your pharmacy may be informed about the fact that you had a surgery and is participating in a research study; however, the research team will not share other information from your study file or medical chart to pharmacists or pharmacy staff.

The Québec Health Record (QHR) (or Le Dossier Santé Québec (DSQ)) will be accessed to collect information about medication prescriptions that you received in clinics/hospitals other than MUHC within 3 months after your surgery.

The study data will be stored for 7 years after the study is completed and then destroyed. Information that is collected online (for example, using your smartphone or computer) will be stored on a secure and encrypted server(REDCap database) protected with firewalls, intrusion detection, and vulnerability scans. If you choose to answer the questionnaires via phone call(s), information collected will be recorded in paper forms and subsequently transferred to the REDCap database. The REDCap database is a secure database with a server hosted at The Research Institute of MUHC.

For monitoring, control, safety, and security your study file as well as your medical charts may be examined by a person mandated by Canadian regulatory authorities, such as Health Canada, as well as the institution, or the Research Ethics Board. All these individuals and organizations adhere to policies on confidentiality. A copy of this consent form will be included in your health records so that members of your healthcare team are aware of your participation in this study. You have the right to consult your study file to verify the information gathered, and to have it corrected if necessary.

COMPENSATION

You will not receive financial compensation for participating in this research study.

SHOULD YOU SUFFER ANY HARM

Should you suffer harm of any kind following any other procedures related to the research study, you will receive the appropriate care and services required by your state of health.

By agreeing to participate in this research project, you are not waiving any of your legal rights nor discharging the study doctor, the sponsor or the institution, of their civil and professional responsibilities.

CONTACT INFORMATION

If you have questions or if you have a problem you think may be related to your participation in this research study, or if you would like to withdraw, you may communicate with the study doctor or with someone on the research team at the If you have any questions regarding the study, you should contact the investigator: Dr. Julio Fiore, Tel.: (514) 934-1934, ext. 47245.

For any question concerning your rights as a research participant taking part in this study or if you have comments, or wish to file a complaint, you may communicate with the Patient Ombudsman at the following phone numbers:

Montreal General Hospital, tel. 514-934-1934, ext. 44285

Royal Victoria Hospital, tel. 514-934-1934, ext. 35655

FUNDING

This project is supported by funds offered by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES).

OVERVIEW OF ETHICAL ASPECTS OF THE RESEARCH

The McGill University Health Centre Research Ethics Board reviewed this research and is responsible for monitoring the study.

Research Study Title: Opioid-free analgesia after outpatient surgery: A pilot randomized controlled trial

SIGNATURES

Signature of the participant

I have reviewed the information and consent form. Both the research study and the information and consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.

I authorize the research study team to have access to my medical record for the purposes of this study.

☐ I authorize the investigators of this research study: to communicate with me directly to ask if I am interested in participating in other research:

Yes ☐ No ☐

Name of participant Signature Date

Signature of the person obtaining consent

I have explained the research study and the terms of this information and consent form to the research participant, and I answered all his/her questions.

Name of the person obtaining consent Signature Date

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INFORMATION AND CONSENT FORM

(Interview with Patients)

Research Study Title:	**Opioid-free analgesia after outpatient surgery: Embedded Qualitative Study**
Protocol number:	2020-5965
Researcher responsible for the research study:	Julio Fiore [1,2]
Co-Investigator(s)/sites:	Liane S. Feldman[1,2], Gabriele Baldini, MD [3]

1. Division of General Surgery, McGill University Health Center, Montreal, Canada
2. Steinberg-Bernstein Center for Minimally Invasive Surgery, McGill University Health Centre, Montreal, Canada
3. Department of Anesthesiology, McGill University Health Center, Montreal, Canada

INTRODUCTION

We are inviting you to take part in this research study because you had a surgery in our hospital. However, before you accept to take part in this study and sign this information and consent form, please take the time to read, understand and carefully examine the following information. You may also want to discuss this study with your family doctor, a family member or a close friend.

This form may contain words that you do not understand. We invite you to speak to your doctor or to other members of the research team, and ask them to explain to you any word or information that is unclear to you before you sign this form.

BACKGROUND

Feeling some pain after surgery is inevitable, and doctors continuously try to find new treatments to keep patients' pain under control. Because the pain process is complex, there are

many varieties of medications that provide pain relief. Pain medications are usually divided into two main groups: opioids and non-opioids. Opioids are drugs that contain chemicals that help relaxing the body and relieving pain. Their use require prescription by a doctor. Non-opioid drugs contain chemicals that relive pain in different ways (for example, by reducing inflammation) and they can be either prescribed by a doctor or purchased over-the-counter in your pharmacy (for example, Tylenol, Advil, Aleve, etc.)

At the moment, the best drug treatment to relief pain after surgery is unknown. We invited you to participate in a study comparing non-opioid medications versus opioid medications to treat pain after surgery. At this time, we would like to kindly invite you to participate in an interview because we would like to understand, from your perspective, the reasons why you agreed (or did not agree) to participate in the study, your experience with pain sensation after surgery and your experience with the pain medications that you took after surgery.

PURPOSE OF RESEARCH STUDY

The goal of this project is gather information about patients experience and thoughts about our study comparing non-opioid medications versus opioid medications to treat pain after surgery and experience with pain sensation and pain medications after surgery. This information will allow clinicians to better understand patients' experience during the study and help developing new programs and interventions aiming to reduce pain after surgery.

DESCRIPTION OF THE RESEARCH PROCEDURES

This research study will take place at McGill University Health Centre (Montreal General Hospital and Royal Victoria Hospital). For this research study, we plan to recruit about 10 participants, men and women over age of 18.

If you agree to participate in this research, you will be invited to participate in an interview (face-to-face or by telephone) with a member of our research team after your operation. This interviewer will ask you questions related to your experience after the operation. The discussion will start with few pre-determined questions (for example: What were your thoughts when you were invited to participate in our study?) but will continue free-flowing to allow you to share your thoughts and ideas. We will audio record the discussions (only your voice), however no identifying questions will be asked during these sessions (for example: you will not be asked about your name or date of surgery etc.). If you agree to participate in this study, we will

schedule the interview within the first 6 weeks after your surgery, at a time that is convenient for you. The interview will be at the hospital (or on the phone) and will take approximately 45 minutes to complete.

Participation in this study will not interfere or modify the standard care given to you.

POSSIBLE RISKS AND DISCOMFORTS

We do not foresee any added risks from participation in this study.

POSSIBLE BENEFITS

You may or may not personally benefit from your participation in this research project. We also hope that the study results will contribute to the advancement of scientific knowledge in this field and help us find better treatments for surgical patients.

OTHER POSSIBLE TREATMENTS

You do not have to take part in this study to receive medical care for your condition. Your access to standard medical information and your treating doctors will be in accordance with our usual practices.

COST AND COMPENSATION

You should not expect any payment or compensation to participate in this study. You will receive up to a maximum of $21.00 to cover the transport costs if you come to the hospital for your interview.

CONFIDENTIALITY

In terms of protecting your anonymity, you can choose a pseudonym for all references made to your comments during the interview. The information that is collected using digital audio recorders (your interview audio) will be transferred to an electronic file. This electronic file will not contain any information (i.e your name, hospital card number) that can be linked to you. The electronic file will be kept on a computer behind the Research Institute MUHC firewall. After the digital interview file is transferred, your interview recording will be immediately deleted from the audio recorder.

The researchers will also collect information from your medical chart to meet the scientific goals of the study. This information will be collected in a research file that may include data

concerning your past and present state of health, your lifestyle information relevant to the surgical procedure (e.g. type of surgery performed, surgery duration etc.). If any complications related to your surgery occur we will collect information about them and details how they were treated. Your research file could also contain other information, such as your name, sex, date of birth and ethnic origin.

All the information collected during the research project will remain strictly confidential to the extent provided by law. To protect your privacy, the information collected for study will be identified only with numbers and/or letters (a code). (Only the investigators of the study will have access to the password protected file that links your personal information (i.e., name, hospital number) to the study code. All electronic data files will be kept on a computer located in the investigator office of the Research institute of MUHC, protected with firewalls, intrusion detection, and vulnerability scans. The study data will be stored for 7 years after the study is completed and then destroyed. Information that is collected online (for example, using your smartphone or computer) will be stored on a secure and encrypted server protected with firewalls, intrusion detection, and vulnerability scans.

For monitoring, control, safety, and security your study file as well as your medical charts may be examined by a person mandated by Canadian regulatory authorities, such as Health Canada, as well as the institution, or the Research Ethics Board. All these individuals and organizations adhere to policies on confidentiality. You have the right to consult your study file to verify the information gathered, and to have it corrected if necessary.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from the project at any time, without giving any reason, by informing the study doctor or a member of the research team.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the study doctor or clinical team.

Your treating doctors, the study doctor, the Research Ethics Board, the funding agency, or the Sponsor may put an end to your participation without your consent. This may happen if new

findings or information indicate that participation is no longer in your interest, if you do not follow study instructions, or if there are administrative reasons to terminate the project.

Any information collected up to the time you withdraw from the study will be stored and may continue to be used in order to maintain the integrity of study data. Please inform the study personnel if you want the data collected up to your withdrawal to be retracted and destroyed. However, any analyses already completed using that data will be kept.

SHOULD YOU SUFFER ANY HARM

Should you suffer harm of any kind following any other procedures related to the research study, you will receive the appropriate care and services required by your state of health.

By agreeing to participate in this research project, you are not waiving any of your legal rights nor discharging the study doctor, the sponsor or the institution, of their civil and professional responsibilities.

CONTACT INFORMATION

If you have questions or if you have a problem you think may be related to your participation in this research study, or if you would like to withdraw, you may communicate with the study doctor or with someone on the research team at the If you have any questions regarding the study, you should contact the investigator: Dr. Julio Fiore, Tel.: (514) 934-1934, ext. 47245.

For any question concerning your rights as a research participant taking part in this study or if you have comments, or wish to file a complaint, you may communicate with the Patient Ombudsman at the following phone numbers:

Montreal General Hospital, tel. 514-934-1934, ext. 44285

Royal Victoria Hospital, tel. 514-934-1934, ext. 35655

FUNDING

This project is supported by funds offered by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES).

OVERVIEW OF ETHICAL ASPECTS OF THE RESEARCH

The McGill University Health Centre Research Ethics Board reviewed this research and is responsible for monitoring the study.

Research Study Title: Opioid-free analgesia after outpatient surgery: Embedded Qualitative Study

SIGNATURES

Signature of the participant

I have reviewed the information and consent form. Both the research study and the information and consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.

I authorize the research study team to have access to my medical record for the purposes of this study.

☐ I authorize the investigators of this research study: to communicate with me directly to ask if I am interested in participating in other research:

Yes ☐ No ☐

Name of participant Signature Date

Signature of the person obtaining consent

I have explained the research study and the terms of this information and consent form to the research participant, and I answered all his/her questions.

Name of the person obtaining consent Signature Date

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INFORMATION AND CONSENT FORM

(Interview with Clinicians)

Research Study Title:	**Opioid-free analgesia after outpatient surgery: Embedded Qualitative Study**
Protocol number:	2020-5965
Researcher responsible for the research study:	Julio Fiore [1,2]
Co-Investigator(s)/sites:	Liane S. Feldman[1,2], Gabriele Baldini, MD [3]

1. Division of General Surgery, McGill University Health Center, Montreal, Canada
2. Steinberg-Bernstein Center for Minimally Invasive Surgery, McGill University Health Centre, Montreal, Canada
3. Department of Anesthesiology, McGill University Health Center, Montreal, Canada

INTRODUCTION

We are inviting you to take part in this research study because you are involved in the care of surgical patients at the McGill University Health Centre. However, before you accept to take part in this study and sign this information and consent form, please take the time to read, understand and carefully examine the following information. We invite you to speak to members of the research team, and ask them to explain any information that is unclear to you before you sign this form.

BACKGROUND

Canada is in the midst of an epidemic of opioid use and abuse fueled by increased prescriptions by physicians. Surgery often serves as the initial event for opioid-naïve patients to obtain a prescription for opioids and spiral into misuse and addiction Decision to prescribe opioids after outpatient surgery largely depends on healthcare culture and surgeon preference. Hence, there

is an urgent need for robust randomized clinical trials (RCTs) to guide clinical decision-making. However, undertaking an RCT of opioid-free analgesia raises important practical concerns including: surgeon and patient preferences about pain treatment with or without opioids, decision regarding participation under preoperative stress, treatment adherence and optimal measurement strategies.

PURPOSE OF RESEARCH STUDY

The aim of this study is to gather insights about clinicians' experiences, perspectives, and potential concerns about patients' involvement in a randomized controlled trial comparing analgesia regimens including opioids versus opioid-free analgesia after outpatient surgery.

DESCRIPTION OF THE RESEARCH PROCEDURES

This research study will take place at McGill University Health Centre [Montreal General Hospital (MGH) and Royal Victoria Hospital (RVH)]. For this study, we plan to recruit about 10 clinicians, but interviews will continue until thematic saturation is reached (i.e. the point after which no further relevant information is elicited).

If you agree to participate in this research, you will be invited to participate in an interview (face-to-face or by telephone) with a member of our research team. This interviewer will ask you questions related to your experience, perspectives and potential concerns about patients' involvement in a randomized controlled trial involving opioid-free analgesia after outpatient surgery. The discussion will start with few pre-determined questions (for example: What were your thoughts when you first heard about the study that we were proposing?) but will continue free-flowing to allow you to share your thoughts and ideas. We will audio record the discussions, however no identifying questions will be asked during these sessions (for example: you will not be asked about your name). If you agree to participate in this study we will schedule the interview at a time convenient for you. The interview will be at the hospital, MGH or RVH, (or on the phone) and will take approximately 45 minutes to complete.

POSSIBLE RISKS AND DISCOMFORTS

We do not foresee any added risks from participation in this study.

POSSIBLE BENEFITS

You may or may not personally benefit from your participation in this research project. We also hope that the study results will contribute to the advancement of scientific knowledge in this field and help us find better treatments for patients.

CONFIDENTIALITY

To protect your anonymity, you can choose a pseudonym for all references made to your comments during the interview. All the information collected about you during the study will remain confidential as the law requires. Your file could also contain other information, such as your name, sex, surgical specialty, years of practice. This information will be kept as a separate list kept by the investigator in charge of the study. To protect your privacy, your information will be identified with a numbers and or letters. Only the investigator in charge of the study knows the numbers and/or letters that link them to you. During your participation in this study, the study team will collect and record information about you in a study file. They will only collect information required to meet the scientific goals of the study. The study data will be stored for 7 years after the study is completed and then destroyed.

For monitoring, control, safety, and security your study file may be examined by a person mandated by Canadian regulatory authorities, such as Health Canada, as well as the institution, or the Research Ethics Board. All these individuals and organizations adhere to policies on confidentiality. You have the right to consult your study file to verify the information gathered, and to have it corrected if necessary.

Results will not be used for evaluation of competence or skill, promotion, or granting of privileges.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from the project at any time, without giving any reason, by informing the research team. Your decision not to participate in the study, or to withdraw from it, will have no impact on your relationship with the clinical team.

The Research Ethics Board, the funding agency, or the Sponsor may put an end to your participation without your consent. This may happen if new findings or information indicate that participation is no longer in your interest, if you do not follow study instructions, or if there are administrative reasons to terminate the project.

Any information collected up to the time you withdraw from the study will be stored and may continue to be used in order to maintain the integrity of study data. Please inform the study personnel if you want the data collected up to your withdrawal to be retracted and destroyed. However, any analyses already completed using that data will be kept.

COMPENSATION

You will not receive financial compensation for participating in this research study.

SHOULD YOU SUFFER ANY HARM

By agreeing to participate in this research project, you are not waiving any of your legal rights nor discharging the study sponsor or the institution, of their civil and professional responsibilities.

CONTACT INFORMATION

If you have questions or if you have a problem you think may be related to your participation in this research study, or if you would like to withdraw, you may communicate with the study doctor or with someone on the research team at the If you have any questions regarding the study, you should contact the investigator: Dr. Julio Fiore, Tel.: (514) 934-1934, ext. 47245.

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OVERVIEW OF ETHICAL ASPECTS OF THE RESEARCH

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Research Study Title: Opioid-free analgesia after outpatient surgery: Embedded Qualitative Study

SIGNATURES

Signature of the participant

I have reviewed the information and consent form. Both the research study and the information and consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.

Name of participant Signature Date

Signature of the person obtaining consent

I have explained the research study and the terms of this information and consent form to the research participant, and I answered all his/her questions.

Name of the person obtaining consent Signature Date

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