PAIN & OPIOID USE OUTCOMES IN KNEE ARTHROPLASTY TRIALS

PAIN AND OPIOID USE OUTCOME MEASURES IN KNEE ARTHROPLASTY RANDOMIZED CONTROLLED TRIALS

By SUSHMITHA PALLAPOTHU, BSc

A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2023) Hamilton, Ontario (Health Research Methodology)

TITLE: Pain and Opioid Use Outcome Measures in Knee Arthroplasty Randomized Controlled Trials

AUTHOR: Sushmitha Pallapothu, BSc (McMaster University)

SUPERVISOR: Dr. Harsha Shanthanna

NUMBER OF PAGES: xii, 85

LAY ABSTRACT

The overarching goal of this thesis is to outline the importance of reporting pain and opioid use as interrelated outcomes, either as multicomponent or co-primary endpoints. Many surgical trials report these outcomes as separate entities, however, trials that assess these two outcomes must consider their conceptual interrelationship. Therefore, we conducted a systematic review to identify pain and opioid use outcome reporting within total knee arthroplasty randomized controlled trials. We also provide an example of a protocol for a multicomponent endpoint (opioid-free pain control) in a trial assessing the efficacy of a multicomponent pain management pathway in patients undergoing total knee arthroplasty. The findings of this thesis suggest that future trials should consider reporting pain and opioid use as either multicomponent or co-primary endpoints using appropriate methods to minimize type I and type II error rates.

ABSTRACT

The primary focus of this thesis is to outline the importance of reporting pain and opioid use as interrelated outcomes either as multicomponent or co-primary endpoints. When more opioids are used, pain intensity can decrease, whereas inadequate analgesia can worsen pain. Trials that emphasize minimizing opioid use can be successful in minimizing opioid consumption, but patients may still suffer from pain. Similarly, trials that focus on decreasing pain could have increased opioid consumption to manage pain. Currently, many surgical trials report these outcomes as separate entities, which can be problematic as these outcome domains are conceptually interrelated. To our knowledge, no previous studies have evaluated the reporting of these two outcomes as interrelated endpoints, as well as the methods used to report them. As one part of this thesis, we conducted a systematic review to identify pain and opioid use reporting within total knee arthroplasty randomized controlled trials. Our review found that only 2.1% of trials reported these outcomes as either multicomponent or co-primary endpoints. In our secondary analysis, 44.7% of trials reported pain as a primary outcome, whereas 32.3% of trials reported opioid use as a primary outcome. We suggest that future trials consider approaches for combining these outcomes while using appropriate methods to minimize type I and type II error rates. As the second part of this thesis, we report a pilot trial protocol of an ongoing study that evaluates pain and opioid use outcomes in total knee arthroplasty patients. In this trial, pain and opioid use at the patient level are combined, as a state of opioid-free pain control, and serves as an example of a multicomponent endpoint.

ACKNOWLEDGEMENTS

Words cannot express my gratitude to my supervisor, Dr. Harsha Shanthanna, and my co-supervisor, Dr. Kim Madden for their invaluable patience, support, and guidance throughout my master's journey. I would also like to express my gratitude to Dr. Lehana Thabane for providing guidance on the progress and future steps of my thesis during committee meetings.

I would also like to acknowledge the undergraduate (Darren Young, Nathasha Rajapaksege, Imad Kashir, Scott Blommaert, Kyle Yau) and master's (Caitlyn Ivany) students who have helped with the screening and data collection stages of the systematic review. Additionally, Caitlyn Ivany assisted with the writing portions of the final thesis draft. Without them, this thesis would not have been completed in such a short timeframe.

Additionally, I would like to thank Dr. Moin Khan for mentoring me throughout my research internship experience. He is an exceptional mentor and teacher and I have learned a lot regarding clinical research and orthopaedics under his supervision.

Finally, I thank my parents, Mahendra Pallapothu and Pushpa Maturi, my sister, Sonya Pallapothu, and my friends, Daizy Beng and Vivienne Lee, for showing immense love and support throughout this journey.

TABLE OF CONTENTS

LIST OF FIGURES

Chapter 2: Pain and Opioid Use Outcome Measures in Knee Arthroplasty Randomized Trials: A Systematic Review

Chapter 3: Opioid Reduction and Enhanced Recovery in Orthopaedic Surgery (OREOS): A Protocol for a Feasibility Randomized Controlled Trial in Knee Replacement Patients

LIST OF TABLES

LIST OF APPENDICES

Chapter 2: Pain and Opioid Use Outcome Measures in Knee Arthroplasty Randomized Trials: A Systematic Review

LIST OF ABBREVIATIONS

AE	Adverse event
AUC	Area under the curve
CBS	Cognitive behavioural skill sessions
CBT	Cognitive behavioural therapy
SMC	Surgical Methods Center
CI	Confidence interval
CPSP	Chronic post-surgical pain
DSMC	Data safety and monitoring committee
EQ-5D-5L	EuroQol-5 Dimensions
ICD-11	Institute for Clinical and Evaluative Sciences
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
MEP	Movement-evoked pain
MMP	ManageMyPain app
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OREOS	Opioid reduction and enhanced recovery in orthopaedic surgery
PAR	Pain at rest
PIPEDA	Personal information protection and electronic documents act
POU	Persistent opioid use
PSH	Perioperative surgical home
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
REB	Research ethics board
REDCap	Research Electronic Data Capture
SAE	Serious adverse event
SIA	Silverman's Integrated Approach
TKA	Total knee arthroplasty

DECLARATION OF ACADEMIC ACHIEVEMENT

Sushmitha Pallapothu drafted all chapters of this thesis. The sole author of this thesis document is Sushmitha, who was involved in all stages of the research project under the supervision of Dr. Harsha Shanthanna, Dr. Kim Madden, and Dr. Lehana Thabane. The supervisors provided edits, comments, and guidance at all stages of this thesis.

The literature search was conducted by Rachel Couban (co-author), librarian, National Pain Centre, McMaster University. The screening and data extraction phases were completed on Covidence (systematic review software).

Study selection and data extraction for the systematic review was carried out by Sushmitha and the co-authors named in Chapter 2. Sushmitha also supervised and trained all of the screeners and extractors, carried out analyses, and drafted the final manuscript, figures, and tables for Chapter 2.

The OREOS trial protocol was conceived by the OREOS Investigators listed in Chapter 3 and was drafted and submitted for publication by Sushmitha to Pilot & Feasibility Studies.

CHAPTER 1: AN INTRODUCTION TO PAIN AND OPIOID USE IN KNEE REPLACEMENT SURGERY

The Burden of Total Knee Arthroplasty

Arthritis is one of the most common chronic diseases in Canada with more than 6 million individuals affected. Over 50% of the population over the age of 65 currently suffer from this disease (1). Arthritis is a complex condition with different aetiologies, such as rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis (OA). OA is more common than all other types of arthritis combined and can cause pain around the knee joints, which can impact a patient's quality of life and function (1, 2). While there are many non-surgical treatments for end-stage knee OA, total knee arthroplasty (TKA; also known as total knee replacement) is considered to be the definitive treatment option. TKA is the second most common surgery in Canada with 43,315 total knee replacements conducted between 2020-2021 (3). While TKA is effective in reducing pain and improving function in most patients, some continue to have lasting pain and disability after surgery. This can be due to factors such as age, gender, psychological elements or post-operative complications such as infection, aseptic loosening, implant design, etc. (4).

Chronic Post-Surgical Pain after TKA

While TKA is effective in managing chronic knee pain and improving function, approximately 8-34% of patients develop chronic post-surgical pain (CPSP) following surgery (5). CPSP is defined as "pain persisting for at least three months after surgery, that was not present before surgery, or that had different characteristics or increased intensity from preoperative pain, localized to the surgical site or a referred area, and other possible causes of pain are excluded (e.g., cancer recurrence, infection, etc.) (6)." CPSP is known

to be associated with a multitude of risk factors, such as preoperative anxiety, depression, pain catastrophizing, age, postoperative pain management, and genetics (7). Based on a systematic review of 11 RCTs, the authors found that 20% of patients developed CPSP three months to five years after TKA (8). The current approach in many institutions for managing postoperative pain, including CPSP, is that each surgeon prescribes a set of pain medications, usually based on surgeon preference and consisting primarily of long- and short-acting opioids. However, this one-size-fits-all approach of opioid prescriptions does not account for individual pain resolution trajectories, patient values, and preferences (9).

Persistent Opioid Use After TKA

In a retrospective cohort study of ~70,000 arthroplasty patients, 13% of opioid-naïve and 62% of chronic opioid users continued to use opioids one year following TKA (10). While opioids are an important part of perioperative pain management in orthopaedic surgery, their potential for long-term adverse effects is concerning (11-13). Although patient-reported pain has remained constant over the years, there has been an increase in prescribing opioids in both orthopaedic and ambulatory settings in the past few decades (14, 15). This rise in prescription opioids and subsequently their use within the patient population has led to addiction, dependence, opioid-related mortality, collectively termed as the "opioid epidemic (16, 17)." While the opioid epidemic is related to a multitude of factors, the increase in opioid prescriptions has majorly contributed to the epidemic (18). Additionally, the prescription of opioids postoperatively can lead to opioid misuse, constipation, nausea, drowsiness, overdose, etc. and can also subsequently lead to persistent

opioid use (POU) (19, 20). POU is defined as "continued opioid prescription use between 90 and 180 days after the surgical procedure in a previously opioid-naïve patient (20, 21)." While opioid prescriptions alone cannot increase the risk of POU in opioid-naïve patients, higher doses and longer durations of prescriptions can (22). In a study conducted by Howard et al., the authors found that patients were at a higher risk of POU when the duration of opioid prescriptions was increased (23). Additionally, in a secondary analysis of a prospective cohort study, Kluger et al. found that patients were at higher risk of POU if patients used opioids 12 months before their surgery, had increased BMI, or had three or more comorbid pain sites (24).

Formulating a Trial to Address the Issues of CPSP and POU

To address the issues of CPSP and POU, a coordinated, personalized, and pragmatic approach needs to be considered. Currently, the Transitional Pain Service (TPS) is being implemented at the Toronto General Hospital (25). This program was implemented to modify pain trajectories within patients who are at risk of developing CPSP, while also minimizing postoperative opioid consumption (25). The TPS program consists of pre- and postoperative scheduled visits with the patient to monitor pain and adjust the pain management plan accordingly (25, 26). Despite the lack of evidence to support its implementation, some issues with the TPS program are that it requires significant costs and personnel, and it does not consider a pragmatic approach to care.

Another example of such programs that address CPSP and POU are perioperative surgical homes (PSH). PSH is a "patient-centered and physician-led multidisciplinary and

team-based system of coordinated care that guides the patient throughout the entire surgical experience," as defined by the American Society of Anesthesiologists (27). This program aims to consider patient preferences and values while also involving other healthcare personnel into any healthcare decisions, rather than just physician-centered care (27). PSH focuses on important aspects such as multimodal analgesia, recovery plans, and nutrition management peri-operatively (27). Similar to the TPS program, PSH also pre-operatively identifies patients who are at high risk for POU and CPSP and provides education on the risks of surgery and anesthesia that are pertinent to the patient (28). Additionally, individualized prescriptions are considered based on the patient's history. In this model, the anesthesiologist is considered to be a "perioperativist" and works with the patient and other members of the patient's circle of care (e.g., surgeons, nurse practitioners) to ensure a seamless transition from pre-admission to discharge (29). The key elements of both TPS and PSH are to collaborate with a multidisciplinary team and engage with the patient to improve their care, satisfaction, and post-operative outcomes (26, 28, 29).

Following the idea of PSH and TPS, we aimed to develop a pragmatic, cost-effective, and scaled-back multicomponent pain management trial known as Opioid Reduction and Enhanced recovery in Orthopaedic Surgery (OREOS). The pain management pathway combines aspects of personalized patient care, shared decision making, risk stratification, patient education, and personalized postoperative prescriptions to enhance patient recovery postoperatively in TKA. The multicomponent pain management pathway will employ a pain management coordinator, who will connect with the patient during all phases of care. The pain management coordinator will additionally

liaise with both the patients and healthcare team to identify a recovery plan and personalized prescriptions best suited for the patient's recovery as well as conduct weekly check-ins postoperatively to identify any issues with pain control, satisfaction, and functional recovery.

An Overview of Pain and Opioid Use Outcomes

RCTs in the arthroplasty field commonly report pain and analgesic consumption outcomes (30). Pain intensity can be reported as continuous (e.g., 0-10), categorical (e.g., mild, moderate, severe), binary (e.g., pain-free (yes/no)), or time-to-event (e.g., time to pain resolution) data. Pain intensity is often measured using validated scales/questionnaires such as the Numerical Rating Scale (NRS), Visual Analog Scale (VAS), Verbal Rating Scale (VRS), etc.

Pain can be measured at both rest and with movement, however, only a small portion of trials report movement-evoked pain (MEP) as an outcome or explicitly state whether pain was measured with movement or at rest (31). Previous studies have shown that adequate analgesic interventions for pain with movement can improve postoperative outcomes. Therefore, Gilron et al., argue that it is important to report MEP when identifying outcomes of interest in surgical trials (31).

Additionally, opioid consumption can be reported as continuous (e.g., total morphine consumption), binary (e.g., rescue analgesia used yes/no), or time-to-event (e.g., time to first rescue analgesia) data (31, 32). In a systematic review conducted by Pogatzki-Zahn et al., commonly reported methods to measure analgesic consumption among

perioperative pain management trials were infused anaesthetic volume, time to first analgesia, morphine equivalents, and frequency of opioid administration/requirements (33).

Rationale For This Thesis

Many trials report both pain and opioid use outcomes with one of them as the primary outcome. However, considering pain and opioid use as separate outcomes is problematic as these outcome domains are conceptually interrelated (31, 32). As more opioids are used, pain scores decrease, whereas inadequate analgesia can worsen pain. Trials that emphasize minimizing opioid use could be successful in decreasing opioids, but the patients could have increased pain. Trials that focus on decreasing pain may have increased opioid use to achieve adequate pain control. Therefore, methods of assessing these two outcomes together or with equal importance need to be considered if the goal is to minimize opioid use while managing pain appropriately.

While there are various methods of reporting pain and opioid use as equally important and interrelated outcomes, many surgical trials, however, report pain and opioids use as separate outcomes. Within the current literature, previous studies have assessed various multi-item measurement tools used in surgical trials, but no studies assessing individual measurement tools such as VAS, NRS, prescription refills, etc., specifically for pain and opioid use outcomes, are available (34, 35). Additionally, to our knowledge, there are no studies that have evaluated the reporting of these two outcomes as interrelated outcomes and the methods used to report them. Therefore, a review of the current literature

to identify pain and opioid use reporting within TKA RCTs as equally important endpoints is of interest. Additionally, we provide an example of a TKA RCT (the OREOS trial) that assesses the effect of a multicomponent pain management pathway on pain and opioid use outcomes using a multicomponent endpoint (opioid-free pain control).

Scope of Thesis

The overarching goal of this thesis is to outline the importance of reporting pain and opioid use as a multicomponent endpoint or as co-primary outcomes to present the conceptual relationship between the two. Chapter 2 is a systematic review describing the different measurement tools used to report pain and opioid use in TKA RCTs, with a particular emphasis on the use of multicomponent or co-primary endpoints assessing both opioid use and pain. Chapter 3 describes the design of an original RCT which aims to assess the efficacy of a multicomponent pain management program using a coordinated approach to improve pain control while minimizing opioid use. The trial protocol is an example of a multicomponent endpoint to report pain and opioid use. Lastly, chapter 4 will conclude with a brief discussion and recommendations.

References

1. 13-10-0096-06 Arthritis, by age group Statistics Canada: Statistics Canada; 2022 [Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310009606.
2. The Truth About Arthritis Arthritis Society Canada: Arthritis Society Canada; [Available from: https://arthritis.ca/about-arthritis/what-is-arthritis/the-truth-about-arthritis.
3. CJRR Annual Report. Ottawa, ON: CIHI: Canadian Institute for Health Information; 2022 2020-2021.
4. Wylde V, Dieppe P, Hewlett S, Learmonth I. Total knee replacement: is it really an effective procedure for all? The Knee. 2007;14(6):417-23.
5. Imai R, Nishigami T, Kubo T, Ishigaki T, Yonemoto Y, Mibu A, et al. Using a postoperative pain trajectory to predict pain at 1 year after total knee arthroplasty. The Knee. 2021;32:194-200.
6. Thapa P, Euasobhon P. Chronic postsurgical pain: current evidence for prevention and management. The Korean journal of pain. 2018;31(3):155-73.
7. Bruce J, Quinlan J. Chronic post surgical pain. Reviews in pain. 2011;5(3):23-9.
8. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ open. 2012;2(1):e000435.
9. Shechter R, Speed TJ, Blume E, Singh S, Williams K, Koch CG, et al. Addressing the opioid crisis one surgical patient at a time: Outcomes of a novel perioperative pain program. American Journal of Medical Quality. 2020;35(1):5-15.
10. Cook DJ, Kaskovich SW, Pirkle SC, Mica MAC, Shi LL, Lee MJ. Benchmarks of duration and magnitude of opioid consumption after total hip and knee arthroplasty: a database analysis of 69,368 patients. The Journal of arthroplasty. 2019;34(4):638-44. e1.
11. Alexander JC, Patel B, Joshi GP. Perioperative use of opioids: current controversies and concerns. Best Practice & Research Clinical Anaesthesiology. 2019;33(3):341-51.
12. Egan TD. Are opioids indispensable for general anaesthesia? British journal of anaesthesia. 2019;122(6):e127-e35.
13. Shanthanna H, Ladha KS, Kehlet H, Joshi GP. Perioperative Opioid AdministrationA Critical Review of Opioid-free versus Opioid-sparing Approaches. Anesthesiology. 2021;134(4):645-59.
14. Morris BJ, Mir HR. The Opioid Epidemic: Impact on Orthopaedic Surgery. JAAOS - Journal of the American Academy of Orthopaedic Surgeons. 2015;23(5).
15. Skolnick P. The opioid epidemic: crisis and solutions. Annu Rev Pharmacol Toxicol. 2018;58(1):143-59.
16. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. Pain and Therapy. 2018;7(1):13-21.
17. Nelson LS, Juurlink DN, Perrone J. Addressing the Opioid Epidemic. JAMA. 2015;314(14):1453-4.

18. Lisa B, Jessica H. Evidence synthesis-The opioid crisis in Canada: a national perspective. Health promotion and chronic disease prevention in Canada: research, policy and practice. 2018;38(6):224.
19. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis research & therapy. 2005;7(5):1-6.
20. Burns S, Urman R, Pian R, Coppes OJM. Reducing new persistent opioid use after surgery: a review of interventions. Current Pain and Headache Reports. 2021;25(5):1-5.
21. Jivraj NK, Raghavji F, Bethell J, Wijeysundera DN, Ladha KS, Bateman BT, et al. Persistent postoperative opioid use: a systematic literature search of definitions and population-based cohort study. Anesthesiology. 2020;132(6):1528-39.
22. Pino CA, Wakeman SE. Prescription of opioids for acute pain in opioid naïve patients. UpToDate. 2021.
23. Howard R, Brown CS, Lai Y-L, Gunaseelan V, Brummett CM, Englesbe M, et al. Postoperative opioid prescribing and new persistent opioid use: the risk of excessive prescribing. Annals of surgery. 2022.
24. Kluger M, Rice D, Borotkanics R, Lewis G, Somogyi A, Barratt D, et al. Factors associated with persistent opioid use 6–12 months after primary total knee arthroplasty. Anaesthesia. 2022;77(8):882-91.
25. Katz J, Weinrib AZ, Clarke H. Chronic postsurgical pain: from risk factor identification to multidisciplinary management at the Toronto General Hospital Transitional Pain Service. Canadian Journal of Pain. 2019;3(2):49-58.
26. Clarke H, Azargive S, Montbriand J, Nicholls J, Sutherland A, Valeeva L, et al. Opioid weaning and pain management in postsurgical patients at the Toronto General Hospital Transitional Pain Service. Canadian Journal of Pain. 2018;2(1):236-47.
27. Kain ZN, Vakharia S, Garson L, Engwall S, Schwarzkopf R, Gupta R, et al. The perioperative surgical home as a future perioperative practice model. Anesthesia & Analgesia. 2014;118(5):1126-30.
28. Vetter TR, Goeddel LA, Boudreaux AM, Hunt TR, Jones KA, Pittet J-F. The Perioperative Surgical Home: how can it make the case so everyone wins? BMC anesthesiology. 2013;13(1):1-11.
29. Vetter TR, Boudreaux AM, Jones KA, Hunter Jr JM, Pittet J-F. The perioperative surgical home: how anesthesiology can collaboratively achieve and leverage the triple aim in health care. Anesthesia & Analgesia. 2014;118(5):1131-6.
30. Bigalke S, Maeßen TV, Schnabel K, Kaiser U, Segelcke D, Meyer-Frießem CH, et al. Assessing outcome in postoperative pain trials: are we missing the point? A systematic review of pain-related outcome domains reported in studies early after total knee arthroplasty. Pain. 2021;162(7):1914-34.
31. Gilron I, Kehlet H, Pogatzki-Zahn E. Current Status and Future Directions of Pain-Related Outcome Measures for Post-Surgical Pain Trials. Can J Pain. 2019;3(2):36-43.
32. Karlsen APH, Pedersen C, Laigaard J, Mathiesen O. Opioid consumption as a core outcome domain in postoperative pain management. Pain. 2022;163(6):e786-e7.
33. Pogatzki-Zahn EM, Liedgens H, Hummelshoj L, Meissner W, Weinmann C, Treede R-D, et al. Developing consensus on core outcome domains for assessing

effectiveness in perioperative pain management: results of the PROMPT/IMI-PainCare Delphi Meeting. Pain. 2021;162(11):2717-36.
34. Wylde V, Bruce J, Beswick A, Elvers K, Gooberman-Hill R. Assessment of chronic postsurgical pain after knee replacement: a systematic review. Arthritis care & research. 2013;65(11):1795-803.
35. Riddle DL, Stratford PW, Bowman DH. Findings of extensive variation in the types of outcome measures used in hip and knee replacement clinical trials: a systematic review. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2008;59(6):876-83.

CHAPTER 2: PAIN AND OPIOID USE OUTCOME MEASURES IN KNEE ARTHROPLASTY RANDOMIZED TRIALS: A SYSTEMATIC REVIEW

Pain and Opioid Use Outcome Measures in Knee Arthroplasty Randomized Trials: A Systematic Review

Sushmitha Pallapothu BSc, MSc (cand), Caitlyn Ivany BSc, MSc (Cand), Imad Kashir BSc (Cand), Scott Blommaert BSc (Cand), Darren Young Shing MD (Cand), Nathasha Rajapaksege BSc (Cand), Kyle Yau BSc (Cand), Rachel Couban MISt, Moin Khan MSc, MD, FRCSC, Lehana Thabane PhD, Kim Madden PhD, Harsha Shanthanna MD, PhD, FRCSC

ABSTRACT

Background: Osteoarthritis (OA) is the most common degenerative joint diseases that occurs in the elderly population. Total knee arthroplasty (TKA) is a recognized treatment for end stage knee OA and is effective in managing pain and improving function. However, postoperative pain and opioid use continue to be major challenges. Trials aiming to study interventions to decrease these interrelated endpoints have used different priorities and varied approaches to measure and report pain and opioid use as clinical outcomes. The purpose of this study was to systematically review randomized controlled trials (RCTs) on TKA to describe the approaches used to measure pain and opioid use. As pain and opioid use are interrelated concepts, we are interested in looking at how studies report and assess them as equal priorities.

Methods: We performed a systematic review of pain and opioid use outcomes used in knee arthroplasty RCTs published from Jan 1, 2012 to Oct 1, 2022. We identified eligible studies using Medline, Embase, and CENTRAL databases. We completed screening and data extraction individually and in duplicate for study inclusion and final analysis. We used Cochrane Risk of Bias 1.0 to assess the methodological quality of the included studies. We reported the final data descriptively.

Results: We included 427 studies in the final analysis which assessed pain and opioid use outcomes in TKA. Of the 427 trials, three studies reported pain and opioid use as a multicomponent endpoint (e.g., time to discharge readiness or block success) and five

studies reported these as co-primary endpoints. In our secondary analysis, we found that 191/427 (44.7%) trials reported pain as a primary outcome, whereas 138/427 (32.3%) trials reported opioid use as a primary outcome.

Discussion: Despite opioid use and pain being conceptually interrelated, our review identified very few studies (2.1%) using pain and opioid use as combined outcomes within RCTs evaluating patient reported outcomes for TKA patients. Future postsurgical pain trials should consider reporting these as combined outcomes when appropriate for their study question.

Funding: No funding was received for this review.

BACKGROUND

Osteoarthritis (OA) is the most common degenerative joint disease worldwide with a global prevalence of 16% for knee OA (1). A common treatment for end-stage knee OA is total knee arthroplasty (TKA) (2). While TKA is effective in managing chronic knee pain and improving function, 20-25% of individuals suffer from ongoing chronic post-surgical pain (CPSP) and dissatisfaction (3). In the context of TKAs, opioids are commonly prescribed to manage acute post-operative pain (3).

While patient-reported pain has remained constant over the years, the number of opioid prescriptions for pain management has increased over the past decade, especially in orthopaedic and ambulatory settings (4, 5). This rise in opioid prescriptions has led to their overuse, addiction and dependence, and an increase in mortality, often collectively termed as the opioid epidemic (6, 7). New strategies to appropriately prescribe opioids within the clinical setting are being implemented, such as personalized pain management programs, education, and multimodal perioperative care (8, 9).

In a recent systematic review of pain-related outcome domains in TKA studies, outcomes such as pain or pain intensity, analgesic consumption, adverse effects, satisfaction, or physical & psychological function were common outcome domains that were reported in 295 randomized controlled trials (RCTs) with pain, analgesic consumption, and adverse effects being more prominent (10). In majority of clinical trials, pain intensity and/or relief are measured with at least one of these outcomes defined as the primary endpoint. Pain intensity is a patient-reported outcome and is usually measured at a particular time point. It can be reported as continuous (e.g., Numerical Rating Scale

(NRS;0-10)), categorical or ordinal (e.g., none, low, moderate, severe), binary (e.g., present or absent), or time-to-event (e.g., time to pain resolution) data. Between movement-evoked pain (MEP) and pain at rest (PAR), greater pain scores have been reported with the former. However, only a small percentage of trials identify this distinction or report MEP as an outcome (11). Opioid use data can be patient-reported or obtained using hospital records or administrative databases via patient-controlled analgesia (PCA), medication diaries, etc. (12, 13). Data can be presented in the form of continuous data (e.g., milligrams of morphine equivalence, etc.), binary (e.g., use of opioids (yes/no)), or time-to-event (e.g., time to first opioid use).

Many trials report one of these outcomes (pain or opioid use) as a primary outcome and relegate the other outcome as a secondary or tertiary outcome. For example, a trial assessing the effect of a medication on pain management post-operatively, can choose to report pain intensity as a primary outcome and morphine consumption as a secondary outcome, or vice versa. Most conclusions are based on the results of the primary outcome (14). However, reporting pain and opioid consumption as separate entities can pose limitations as these outcomes are conceptually interrelated (12, 13). In this context, the concept of interrelatedness can be illustrated through the indirect proportional relationship between opioid use and pain (e.g., as more opioids are used, pain scores decrease, whereas inadequate analgesia can worsen pain). This highlights how these two outcomes are synergistic and should be considered as interconnected endpoints.

There are several options for trial investigators to report primary outcomes as important endpoints such as 1) co-primary outcomes; 2) multicomponent endpoints; or as

3) composite endpoints (15). When two or more outcomes are separately reported and analyzed, but with equal importance, they are known as co-primary outcomes. A multicomponent endpoint consists of two or more components and a participant must meet all individual components to meet the study endpoint (e.g., discharge readiness). Lastly, composite endpoints combine several events into a single outcome but an effect on at least one of the components counts as meeting the study endpoint. Using multiple outcomes poses methodological challenges, such as multiplicity which occurs when multiple comparisons inflate the type I error rate (15, 16). To address this challenge, appropriate statistical adjustments for multiplicity must be determined *a priori*. In contrast, co-primary outcomes can reduce the power of the study (inflation of the type II error rate) and appropriate adjustments to the sample size are needed to maintain study power (15).

Previous studies have outlined potential analytical approaches to combine and report pain scores and opioid use, but most arthroplasty trials continue to report these two outcomes individually (17-20). The purpose of this study is to systematically review pain and opioid use outcome reporting during the immediate postoperative period and as medium-to-long term outcomes (> 3 months after surgery) in published RCTs on TKA.

Objectives

1. To identify the number of trials reporting both pain intensity and opioid use as primary outcomes, either as co-primary or a multicomponent outcome.
2. To describe and report the approaches used to assess them as co-primary or multicomponent endpoints.

3. To describe the approach used to measure and report pain intensity: primary or secondary outcome; continuous, categorical, or time-to-event outcome; scale or approach used (such as 0-10 NRS); recall instructions to participants (e.g., pain now, average pain, maximum pain, etc.); time points measured; and minimum important difference (MID) considered for sample size determination (if applicable).
4. To describe the approach used to measure and report opioid use: primary or secondary outcome; type of measurement (e.g., continuous, binary, time-to-event); approach to measurement (e.g., medical records, administrative databases, pain diaries, etc.); time points measured; and MID considered for sample size determination (if applicable).

METHODS

Eligibility Criteria

We included any RCTs on adult patients (>18 years) undergoing TKA and assessed postsurgical pain and opioid use as either primary or secondary outcomes. In the case of studies involving more than one type of arthroplasty (e.g., hip, shoulder, or unicompartmental knee arthroplasty (UKA)), we included the study if the population was >50% TKA. We excluded any studies that were published in a language other than English, any animal or pre-clinical studies, conference abstracts without a full-text article, or protocol papers and ongoing studies without published results.

Information Sources

We identified all relevant and recent RCTs through a systematic search of Embase, Medline, and CENTRAL, from January 1, 2012, of each database to October 1, 2022, to identify studies that reported pain and opioid use outcomes in TKA. We limited the search to the past 10 years to capture trial reporting pertinent to the ongoing opioid epidemic (21).

Search Strategy

We developed a systematic search strategy for each database with the assistance of an experienced librarian. The full strategy for MEDLINE can be found in Appendix 1.

Selection Process

We used a systematic review management software, Covidence (www.covidence.org), to conduct the title and abstract, and full-text phases of the screening process. At the title and abstract phase, we included a study if at least one reviewer decided to include it. Prior to the full-text screening, we conducted a pilot test was conducted using a random sample of ten studies to ensure consistency among reviewers. Each study was reviewed by two reviewers in the full-text stage. We resolved disagreements among reviewer pairs through discussion and/or by involvement of a third reviewer, until we reached consensus.

Data Collection Process

We developed a study-specific data extraction form and ran a pilot test with a random sample of five studies on Covidence. Reviewers extracted data independently, and in duplicate. Reviewer pairs cross checked the data for accuracy and consensus, prior to considering for analysis. Any disagreements were resolved among a pair, with the first author resolving conflicts.

Data Items

Extracted variables included study characteristics (e.g., author, year, country, treatment type, follow-up duration, funding, anesthesia type, number of treatment arms), methodological characteristics (e.g., trial design, sample size, MID), and the outcomes of interest (co-primary vs. multicomponent endpoints and description of how they are reported, timepoints, types of measurement, etc.).

We collected postsurgical pain and opioid use outcomes. The following were our outcomes of interest:

Primary Outcomes:

- Number of trials that report pain and opioid use as co-primary or multicomponent outcomes.
- Approach used to assess and report pain and opioid use as a co-primary or multicomponent outcome.

Secondary Outcomes:

Pain Outcomes:

- Number of trials reporting pain as a primary outcome.
- Descriptive reporting of how pain was measured: continuous, categorical, or time-to-event.
- Descriptive reporting of recall instructions to patients (e.g., pain at rest or movement, average pain, current pain, etc.)
- Descriptive reporting of measured time points after surgery.
- Descriptive reporting of MID for sample size determination (if applicable).

Opioid Outcomes:

- Number of trials reporting opioid use as a primary outcome.
- Descriptive reporting of how opioid use was measured: continuous, binary, time-to-event.
- Descriptive reporting of how opioid use was obtained (e.g., medical records, pain diaries, administrative databases, etc.).
- Descriptive reporting of measured time points after surgery.
- Descriptive reporting of MID for sample size determination (if applicable).

Study Risk of Bias Assessment

Author pairs independently graded the methodological quality of each included study using the Cochrane 1.0 risk of bias tool on Covidence which addressed aspects such as selection, performance, detection, attrition, and reporting biases (22).

Synthesis and Reporting

Descriptive statistics such as frequencies, means, and standard deviations were used to summarize the study characteristics. We presented the frequency data as percentages when we described the use of reported outcomes and MID. Approaches used to measure pain and opioid use as co-primary or multicomponent outcomes were described narratively.

We reported the duration of follow-up as very short-term postoperative period (≤ 3 days), short-term (4 days – 3 months), or medium to long-term (≥ 3 months after surgery). We categorized interventions for pain management as nerve blocks, local infiltration analgesia, and pain medications. Other interventions were classified into either rehabilitation, anesthetic technique (general vs. neuraxial), surgical techniques, device, education, or other. Timing of intervention was identified as pre-, intra-, or post-operative, with intra-operative defined as any treatment that occurred from skin incision to skin closure.

RESULTS

Study Selection

We identified 31,317 citations from three primary databases [MEDLINE n=11,585; EMBASE n=15,449; CENTRAL n=4,282]. After all phases of screening were completed, 427 studies were included for data extraction and analysis. A detailed PRISMA flow diagram outlining the main reasons for exclusions and number of studies included at each stage is provided in Figure 1.

Study Characteristics

All studies in this systematic review were RCTs on TKA that assessed pain and opioid use outcomes. Most trials were conducted in Asia (179/427; 41.9%) or North America (131/427; 30.7). Most had a parallel design (424/427; 99.3%), with one of them as a cluster RCT and three were crossover RCTs (3/427; 0.7%). Additionally, eight of the included trials were pilot studies. The mean sample size was 104.7 (SD 85.4). Among studies that reported funding (290/427; 67.9%), majority were non-industry funded (51.4%). Studies primarily assessed outcomes in a very short time frame (≤ 3 days postoperatively; 226/427; 52.9%), with 118 (27.6%) and 83 (19.4%) trials assessing outcomes of interest between 4 days to 3 months or ≥ 3 months, respectively. Majority compared pain management treatments (352/427; 82.4%) either pre- (169/427; 39.6%), intra- (198/427; 46.7%), or postoperatively (181/427; 42.4%). Additional details of the study characteristics are provided in Table 1.

Risk of Bias in Studies

The risk of bias across studies is shown in a summary diagram in Figure 2. Most studies reported low risk of bias for random sequence generation, allocation concealment, and incomplete outcome data. Blinding of participants and personnel, blinding of outcome assessors, and selective reporting were the most concerning for risk of bias as many studies had unclear or high risk of bias.

Primary Outcome Analysis

Multicomponent Outcomes

Three papers reported pain and opioid use as a multicomponent outcome (23-25). Zhang et al., was a three-arm parallel RCT which compared three different doses of ropivacaine for a continuous femoral nerve block (24). The primary outcome was time to discharge readiness, defined as mean pain score at rest and with movement <4 (0-10), independence from intravenous and rescue opioids in the previous 12 hours, and ambulation of at least 30 meters, reported in days (24). Similarly, Machi et al., also reported time to discharge readiness as their primary outcome, reported in hours (25). The following criteria had to be fulfilled to meet the primary endpoint: 1) adequate analgesia (mean pain scores at rest <4 using NRS (0-10); 2) independence from intravenous opioids for at least 12 hours; 3) ability to stand, walk 3 meters, walk back, and sit down independently (Timed Up and Go test); and 4) unassisted ambulation of at least 30 meters evaluated using the 6-minute walk test (25). Lastly, Wang et al., identified block success as their primary outcome, which consisted of pain scores at rest <3 using NRS (0-1) and <5 during movement, as well as no rescue analgesia requirements within the first 6 hours following TKA (23). Block success was reported as a binary outcome (23).” Another trial identified pain and opioid use as a combined outcome (pain free time) (26). Pain free time was defined as time since analgesic administration immediately after surgery (0 hours) and up to the administration of a morphine rescue dose with a Visual Analog Scale (VAS) pain score ≤ 3 (0-10). The endpoint was reported as both a continuous variable and as a proportion (26).

Three of the four paper that reported the outcome of interest as multicomponent endpoints, reported these outcomes as dichotomous data (23-25). In the trials which reported time to discharge or block success, cut-offs were set for pain scores and opioid

consumption (e.g., pain score < 3 using VAS) and patients who met each threshold were considered to have reached the endpoint.

Co-Primary Outcomes

Five papers reported pain and opioid use as co-primary outcomes (27-31). In the first study, local infiltration analgesia (LIA) with liposomal bupivacaine was compared with LIA alone. Mont et al., compared pain using VAS with an area under the curve (AUC) between 12-48 hours and total opioid consumption from 0 to 48 hours (27). The co-primary endpoints were assessed using analysis of variance. AUC VAS pain scores were compared between the two interventions using a one-tailed test ($\alpha = 0.025$) (27). If VAS pain intensity AUC was statistically significant, opioid consumption was then also tested at 0.025 (one-sided). If an effect of the treatment was shown on both of the co-primary endpoints, the secondary efficacy endpoints were assessed using a hierarchical, fixed sequence, sequentially rejective approach (27). Three studies used a joint hypothesis test to evaluate their outcomes (29-31). Rawal et al., compared etoricoxib (90 or 120 mg), ibuprofen, or placebo (28). The co-primary outcomes of this trial were average pain intensity difference at rest (NRS) from days 1-3 postoperatively and average daily morphine consumption from days 1 to 3 (28). First, the authors compared the effects of a 120mg etoricoxib dose with the placebo on each of the co-primary endpoints. If 120mg of etoricoxib was superior to placebo on each of the co-primary endpoints ($\alpha = 0.05$, two-sided), only then was the 90mg dose compared against placebo ($\alpha = 0.05$, two-sided) (28). Since both of the etoricoxib doses had to show an effect on both of the co-primary outcomes to show superiority to

placebo, the step-down testing procedure controlled the type I error rate (multiplicity) at 5% by splitting the α (28). The co-primary endpoints in Kim et al., were identified as such: quadriceps muscle strength, pain scores, and total opioid consumption to compare an adductor canal block (ACB) against a femoral nerve block (FNB) (29). Quadriceps muscle strength (measured using a dynamometer), pain intensity (NRS), and opioid consumption were assessed from 6 to 8 hours, postoperatively (29). A two-step sequential testing procedure was conducted where non-inferiority on all co-primary outcomes was tested first, followed by a superiority test. The outcomes were tested as multiple primary endpoints for the superiority test. ACB was considered superior to FNB if effects were shown on at least one of the primary outcomes, specifically quadriceps strength (29). Each endpoint was tested at $\alpha=0.025$ (one-sided t-test) for non-inferiority and $\alpha=0.008$ [splitting the α by 3 (for each of the three outcomes)] for the superiority test. The Holm-Bonferroni stepdown procedure was used to control for the family-wise error rate for the superiority test (29). In Yadeau et al., duloxetine and placebo groups were compared (30). If both of the co-primary endpoints (pain intensity and opioid consumption) were non-inferior within the duloxetine group, only then was superiority tested. In the superiority test, if duloxetine showed effects on either one of the outcomes, then duloxetine was favoured (30). The endpoints were tested at $\alpha=0.025$ (one-sided two-sample t-test) for non-inferiority, whereas the superiority test was performed at $\alpha = 0.017$ (one-sided two-sample t-test). A Bonferroni adjustment was used to correct for multiplicity for the superiority test (30). Lastly, Farag et al., tested the non-inferiority of the interventions on all co-primary outcomes (pain intensity and cumulative morphine consumption) first, followed by a superiority test (31). The authors

did not make any adjustments to the significance criteria as the treatment had to show effects on both outcomes to claim superiority. Each co-primary outcome was tested at $\alpha = 0.025$ (one-sided t-tailed test) (31). A summary of the study characteristics for the primary outcome analyses are outlined in Table 2.

Of the trials that reported co-primary outcomes, we found that various methods, such as the joint hypothesis test, serial gatekeeping, and step-down procedures were used to assess the efficacy of the treatment on the co-primary endpoints. In these trials, there were no problems of multiplicity when testing the co-primary endpoints, but appropriate adjustments were made to the secondary endpoint tests using the Holm and Bonferroni methods. Since an effect has to be shown on both of the co-primary endpoints, the overall alpha was split among the co-primary endpoints to accommodate for the loss of power.

Secondary Outcome Analysis

Pain was reported as a primary outcome in 191 (44.7%) studies while 236 (55.3%) studies reported it as a secondary outcome. Most studies reported pain using continuous data (426/427; 99.8%), whereas only 12 (2.8%) and 1 (0.2%) study reported pain using categorical and time-to-event data, respectively. VAS (60.9%) and NRS (29.0%) were the most frequently used tools to measure pain. Common instructions used to obtain pain were "current pain" (137/427; 32.1%) or pain at rest and movement (184/427; 43.1%). Pain was primarily recorded using a questionnaire (421/427; 98.6%). Pain outcomes alone were often assessed within 3 days (very short follow-up) following total knee arthroplasty (410/427; 96.1%) or between 4 days and 3 months (short follow-up; 128/427; 30.0%). Only 60

(31.4%) trials reported MID for pain within their sample size calculation in studies where pain was reported as a primary outcome.

Opioid use was reported as a primary outcome in 138 (32.3%) studies while 289 (67.7%) studies reported it as a secondary outcome. Most studies reported opioid use as continuous measurements (411/427; 96.3%), while 46 (10.8%) reported this outcome as a binary measurement. Opioid use was primarily recorded/obtained from medical records (408/427; 95.6%) or medication diaries (31/427; 4.9%). Most studies measured opioid use within 3 days post-operatively (380/427; 89.0%) or within 3 months (63/427; 14.8%) following TKA. Only 29 (21.0%) trials reported MID for opioid consumption within their sample size calculation in studies that reported opioid use as a primary outcome. Additional details of the secondary outcome analysis are outlined in Table 3.

DISCUSSION

The purpose of our study was to systematically review RCTs on TKA which report pain and opioid use and evaluate how investigators report these outcomes. Our results found that only 2.1% of trials reported these outcomes using a combination of outcomes to capture pain and opioid use, whereas 98% of the included trials reported these outcomes as separate entities. In the trials that reported these outcomes as separate entities. Trials assessing different pain management strategies following TKA may want to consider both pain and opioid use as primary outcomes as patients usually suffer from moderate to severe pain and hence rely on opioids during recovery. Measurement of one outcome, such as pain, without accounting for the change in the use of opioids would provide incomplete

information because use of opioids can be patient dependent and differentially affect pain intensity. Among the trials that reported pain and opioid use as either co-primary or multicomponent endpoints, outcomes were only assessed in the short term (< 3 months). Future trials should consider assessing these outcomes in the long-term (>3 months) as it would be useful to assess how many patients develop CPSP three months post-operation.

Of the papers that reported pain and opioid use outcomes as multicomponent endpoints, the outcomes were reported as dichotomous data (23-25). While dichotomizing continuous data can simplify the statistical analysis and presentation and interpretation of results, a limitation is that it can lead to a loss of information due to reduction of data (32). Furthermore, in the two studies that assessed time to discharge, other components such as the 6-minute walk test were included (24, 25). While the addition of different components to a multicomponent endpoint depends on the study objectives and treatments that are assessed, the inclusion of more components can decrease the chances of reaching the endpoint/event.

When using co-primary endpoints, increasing the alpha for each of the co-primary endpoints is not acceptable as it may undermine the ability to interpret a treatment effect on each of the co-primary outcomes (15). Future studies should consider splitting the overall alpha among the co-primary endpoints to prevent inflation of the type I error rate.

Our systematic review highlights that various combinations of measurement tools and recall instructions are used among trials. Currently, there is discussion about the need to develop core outcome sets for pain research that encompass pain intensity, pain interference, pain and physical functioning, temporal aspects of pain, description of pain,

emotional characteristics, use of pain medications, and improvement and satisfaction with pain relief (33-35). In a study conducted by Wylde et al., pain features within each domain were identified (e.g., pain intensity: average pain, worst pain, controllable pain) (34). While core outcome sets are helpful in guiding authors on the various methods and tools that can be used to assess pain qualities, a one-size-fits-all approach may not be applicable to all postsurgical pain trials as outcomes are determined based on the type of treatment and objectives of the trial.

The results of our review are limited by several factors, one of which is that we only included studies published in English which limited our assessment of study outcomes that may be reported in articles published in other languages. In the context of risk of bias analysis, any judgements noted as "unclear" were not further clarified with study authors. Additionally, majority of the included studies were of low-quality evidence, in the context of selective outcome reporting and blinding when we assessed risk of bias. Higher quality evidence is needed to support the results of this systematic review. Lastly, we only chose to include studies that focused primarily on TKA which limited the generalizability of the results. Future reviews should consider assessing all types of knee arthroplasties (unicompartmental, patellofemoral, etc.).

Despite the limitations, our study encompasses a rigorous review of the current literature from RCTs surrounding postoperative pain and opioid use. To ensure accuracy, aspects of this review were completed in duplicate including study inclusion, screening, quality assessment, and data extraction. Additionally, to our knowledge, this study is the first systematic review that assesses the frequency of combined endpoints in the context of

pain and opioid use outcomes, utilized in TKA RCTs. As such, this review highlights necessary study aspects and measures that are needed for future research.

Conclusion

In conclusion, there are limited studies which consider pain and opioid use as explicitly interrelated outcomes in TKA trials. We suggest that future trials that assess pain management strategies and involve pain and opioid use as outcomes, consider combining these as either multicomponent or co-primary endpoints. Based on the study design and other attributes, trials should use appropriate methods to combine either continuous or dichotomous outcomes ensuring measures to minimize type I and type II error rates.

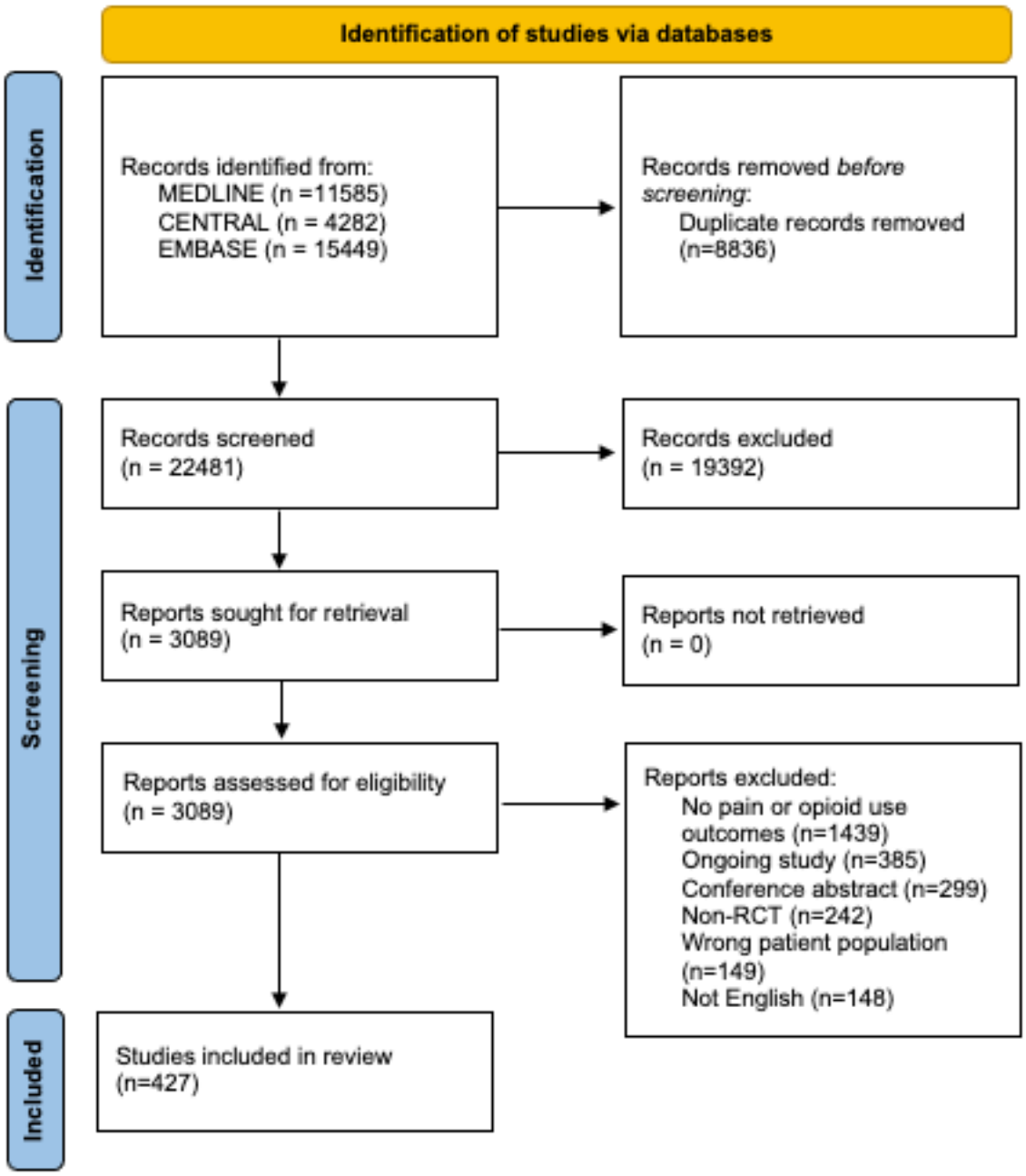

Figure 1: PRISMA flow diagram.

Table 1: Study Characteristics

Study Characteristics	n=427
Year of Publication, n (%)	
2011	11 (2.6)
2012	25 (5.9)
2013	30 (7.0)
2014	26 (6.1)
2015	37 (8.7)
2016	35 (8.2)
2017	35 (8.2)
2018	43 (10.1)
2019	42 (9.8)
2020	44 (10.3)
2021	52 (12.2)
2022	50 (11.7)
Country, n (%)	
Asia	179 (41.9)
North America	131 (30.7)
Europe	93 (21.8)
Australia	11 (2.6)
Africa	8 (1.9)
South America	5 (1.2)
Not reported	5 (1.2)
Unclear	1 (0.2)
Trial Design, n (%)	
Parallel	424 (99.3)
Crossover	3 (0.7)
Cluster	1 (0.2)
Funding, n (%)	
Not-for-profit	149 (34.9)
For-profit	19 (2.1)
Both	7 (1.6)
Not funded	115 (26.9)
Not reported	137 (32.1)
Sample Size, n (%)	
≤ 100	285 (66.7)
101-500	138 (32.3)
> 500	4 (0.9)
Mean sample size (SD)	104.72 (85.4)
Overall Follow-Up Duration, n (%)	
Very Short Follow-up (≤ 3 days)	226 (52.9)
Short Follow-up (4 days-3 months)	118 (27.6)
Medium-Long Follow-up (≥ 3 months)	83 (19.4)

Population, n (%) *	
TKA only	411 (96.3)
TKA & THA	14 (3.3)
TKA & UKA	2 (0.5)
Number of Treatment Arms, n (%)	
2 arms	325 (76.1)
3 arms	83 (19.4)
> 3 arms	19 (4.4)
Type of Treatment, n (%)	
Pain Management	352 (82.4)
Rehabilitation	5 (1.2)
Anesthetic Technique	24 (5.6)
Surgical Technique	14 (3.3)
Device	3 (0.7)
Education	6 (1.4)
Other	41 (9.6)
Anesthesia Type, n (%)	
General Anesthesia	145 (34.0)
Neuraxial (Spinal or Epidural)	279 (65.3)
Not reported	43 (10.1)
Administration of Treatment, n (%)	
Preoperative	169 (39.6)
Intraoperative	198 (46.4)
Postoperative	181 (42.4)
Treatment was administered at more than one of the above time points	112 (26.2)

***TKA:** total knee arthroplasty; **THA:** total hip arthroplasty; **UKA:** unicompartmental knee arthroplasty

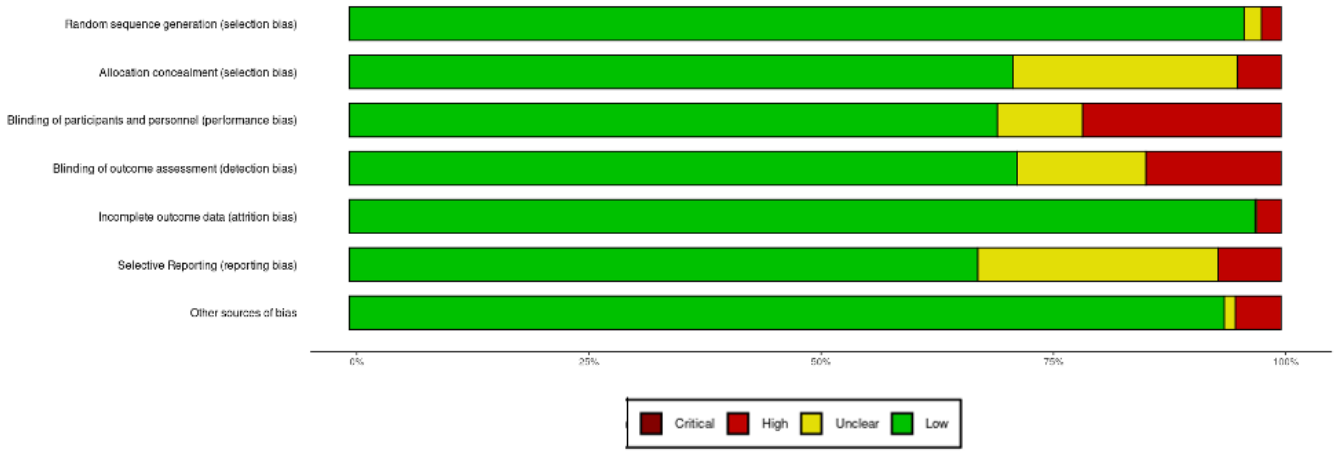

Figure 2: Summary of risk of bias of included studies

Table 2: Primary outcome analyses (multicomponent and co-primary outcomes)

Study	Interventions	Description of Analysis	Pain Outcomes	Opioid Use Outcomes
Multicomponent Outcomes				
Zhang 2020 (24)	0.1%, 0.15%, or 0.2% of ropivacaine for a continuous femoral block	Discharge readiness: Pain scores < 4, independence from intravenous and rescue opioids in the previous 12 hours, and ambulation of at least 30 meters.	Pain was measured using NRS both at rest and with movement with a questionnaire. No MID was reported for pain.	Opioid use was measured using medical records. Total intravenous morphine from 0-48 hours was assessed. No MID was reported for opioid use.
Machi 2015 (25)	ACB versus FNB	Discharge readiness: pain scores <4, independence from intravenous and rescue opioids for at least 24 hours post-operatively, ability to stand and sit down on their own (timed up and go test), and unassisted ambulation for at least 30 meters (6-minute walk test).	Pain at rest was measured using NRS every 4 hours using a questionnaire. No MID was reported for pain.	Opioid use was measured using medical records. Number of patients that were opioid-free for 12 hours was assessed. Total morphine consumption was also recorded over 96 hours. No MID was reported for opioid use.
Wang 2020 (23)	ACB versus IPACK	Block success: defined as pain <3 during rest and <5 during movement and no rescue analgesia within 6 hours following TKA.	Pain at rest was assessed using NRS in the recovery room, 2, 4, and 6 hours after surgery using a questionnaire. No MID was reported.	Opioid use was obtained from the patient's medical records and was assessed as patients receiving rescue analgesia (yes/no) within 6 hours after completing surgery. No MID was reported.

Nicolino 2020 (26)	PIA only versus PIA plus peripheral saphenous nerve block	Pain free time: time since analgesic administration immediately after surgery, up to the administration of a morphine rescue dose for a VAS pain score ≤ 3/10	Pain at rest was measured using NRS every 4 hours using a questionnaire. No MID was reported.	Opioid use was obtained from medical records. Number of rescue medication doses were recorded at 24 and 48 hours, post-operatively. No MID was reported.
Co-Primary Outcomes				
Mont 2018 (27)	LIA with liposomal bupivacaine versus LIA with bupivacaine HCl	The co-primary outcomes were defined as the area under the curve for VAS pain scores 12-48 hours and total opioid consumption 0-48 hours after TKA.	Pain intensity was measured using VAS between 12-48 hours after surgery. No MID was reported.	Total opioid consumption was obtained from the patient's medical records between 0-48 hours after surgery. No MID was reported.
Rawal 2013 (28)	Etoricoxib versus ibuprofen versus placebo	The co-primary endpoints included average pain using the NRS and total daily morphine dose over 1-3 days following TKA.	Average pain scores at rest were assessed using NRS over days 1 to 3 post-operatively using a questionnaire. Secondary outcomes included change in pain at rest from baseline to 4-7 days and pain with movement over days 4-7. The MID for pain at rest was considered to be	Total daily morphine use was obtained from the patient's medical records. No MID was reported.

			2 points on the NRS.	
Kim 2014 (29)	ACB versus FNB	The co-primary endpoints included quadriceps muscle strength, pain scores, and total opioid consumption measured from 6 to 8 hours, post-operatively.	Pain intensity was assessed using NRS at 6 and 8 hours, post-operatively. No MID was reported for pain intensity.	Total opioid consumption was obtained from medical records for 6-8 hours post-operation. No MID was reported for opioid use.
YaDeau 2022 (30)	Duloxetine versus placebo	The co-primary endpoints were pain intensity (NRS) with movement (POD 1, 2, 14) and cumulative morphine consumption (0-14).	Pain intensity was measured using NRS with movement on POD1, POD2, and POD14.	Cumulative morphine consumption was obtained from medical records for POD0-14. The MID for opioid consumption within the superiority test was 25% (108.1 mg).
Farag 2014 (31)	Femoral nerve catheter guidance either by 1) ultrasound; 2) ultrasound + electrical stimulation via the needle; 3) ultrasound + electrical stimulation via the needle and catheter	The co-primary endpoints were pain intensity using VRS and cumulative morphine consumption within the first 48 hours after TKA.	Pain was measured using VRS every 30 minutes in recovery and every 4 hours for 48 hours using a questionnaire. No MID was reported for pain.	Opioid use was measured using medical records. Cumulative opioid use was measured from 0-48 hours. No MID was reported for opioid use.

ACB: adductor canal block; **FNB:** femoral nerve block; **PIA:** periarticular infiltration;

LIA: local infiltration analgesia; **IPACK:** infiltration of the popliteal artery and capsule of

the posterior knee; **POD:** post-operative day; **VRS:** verbal response scale; **NRS:** numerical rating scale.

Table 3: Secondary outcome analyses

	Overall n=427
Pain Outcomes	
Was pain a primary outcome?, n(%)	
Yes	191 (44.7)
No	236 (55.3)
Was the measurement reported as either continuous, categorical, or time-to-event? (multiple options can be chosen), n(%)	
Continuous	426 (99.8)
Categorical	12 (2.8)
Time-to-Event	1 (0.2)
What tool was used to report pain? (multiple options can be chosen), n(%)	
VAS	260 (60.9)
NRS	124 (29.0)
VNRS	14 (3.3)
WOMAC Pain subscale	4 (0.9)
McGill Pain	2 (0.5)
BPI Pain Severity	3 (0.7)
Other	19 (4.4)
Not Reported	8 (1.9)
What instructions were used to obtain pain measurements? (multiple options can be chosen), n(%)	
Current pain	137 (32.1)
Pain at rest	53 (12.4)
Pain with movement	34 (8.0)
Pain at rest & movement	184 (43.1)
Average pain	27 (6.3)
Maximum pain	41 (9.6)
Minimum pain	7 (1.6)
Pain during sleep	11 (2.6)
Other	19 (4.4)
How was pain recorded? (multiple options can be chosen), n(%)	
Questionnaire	421 (98.6)
Pain diary	8 (1.9)
Not reported	1 (0.23)
When was pain measured (all time points)? (multiple options can be chosen), n(%)	
Very short period (≤ 3 days)	407 (95.3)
Short period (4 days-3 months)	128 (30.0)
Medium-long period (≥ 3 months)	47 (11.0)
Discharge (unspecified)	3 (0.7)

Was MID reported for studies that reported pain as a primary outcome?, n(%)	
Yes	60 (31.4)
No	131 (68.6)
Opioid Use Outcomes	
What opioid use a primary outcome?, n(%)	
Yes	138 (32.3)
No	289 (67.7)
Was opioid use reported as continuous, binary, or time-to-event? (multiple options can be chosen), n(%)	
Continuous	411 (96.3)
Binary	46 (10.8)
Time-to-event	37 (8.7)
How was opioid use measured? (multiple options can be chosen), n(%)	
Medical records	408 (95.6)
Diaries	31 (4.9)
Prescription refills (unspecified)	4 (0.9)
Population database	2 (0.5)
Not reported	3 (0.7)
When was opioid use measured (all time points)? (multiple options can be chosen), n(%)	
Very short period (≤ 3 days)	380 (89.0)
Short period (4 days-3 months)	63 (14.8)
Medium-long period (≥ 3 months)	9 (2.1)
Discharge (unspecified)	13 (3.0)
Was MID reported for studies that reported opioid use as a primary outcome?, n(%)	
Yes	29 (21.0)
No	109 (79.0)

REFERENCES

1. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. eClinicalMedicine. 2020;29.
2. Lespasio MJ, Piuzzi NS, Husni ME, Muschler GF, Guarino A, Mont MA. Knee Osteoarthritis: A Primer. Perm J. 2017;21:16-183.
3. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ open. 2012;2(1):e000435.
4. Morris BJ, Mir HR. The Opioid Epidemic: Impact on Orthopaedic Surgery. JAAOS - Journal of the American Academy of Orthopaedic Surgeons. 2015;23(5).
5. Skolnick P. The opioid epidemic: crisis and solutions. Annu Rev Pharmacol Toxicol. 2018;58(1):143-59.
6. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. Pain and Therapy. 2018;7(1):13-21.
7. Nelson LS, Juurlink DN, Perrone J. Addressing the Opioid Epidemic. JAMA. 2015;314(14):1453-4.
8. Labrum JTIV, Ilyas AM. The Opioid Epidemic: Postoperative Pain Management Strategies in Orthopaedics. JBJS Reviews. 2017;5(8).
9. Everson M, McLain N, Collins MJ, Rayborn M. Perioperative Pain Management Strategies in the Age of an Opioid Epidemic. Journal of PeriAnesthesia Nursing. 2020;35(4):347-52.
10. Bigalke S, Maeßen TV, Schnabel K, Kaiser U, Segelcke D, Meyer-Frießem CH, et al. Assessing outcome in postoperative pain trials: are we missing the point? A systematic review of pain-related outcome domains reported in studies early after total knee arthroplasty. Pain. 2021;162(7):1914-34.
11. Srikandarajah S, Gilron I. Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: A fundamental distinction requiring standardized measurement. Pain. 2011;152(8).
12. Gilron I, Kehlet H, Pogatzki-Zahn E. Current Status and Future Directions of Pain-Related Outcome Measures for Post-Surgical Pain Trials. Can J Pain. 2019;3(2):36-43.
13. Karlsen APH, Pedersen C, Laigaard J, Mathiesen O. Opioid consumption as a core outcome domain in postoperative pain management. Pain. 2022;163(6):e786-e7.
14. Mascha EJ, Turan A. Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. Anesthesia & Analgesia. 2012;114(6):1304-17.
15. Multiple Endpoints in Clinical Trials Guidance for Industry FDA: FDA; 2017 [updated 08/24/2018. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/multiple-endpoints-clinical-trials-guidance-industry.
16. Qian Y, Walters SJ, Jacques R, Flight L. Comprehensive review of statistical methods for analysing patient-reported outcomes (PROs) used as primary outcomes in

randomised controlled trials (RCTs) published by the UK's Health Technology Assessment (HTA) journal (1997–2020). BMJ Open. 2021;11(9):e051673.
17. Dai F, Silverman DG, Chelly JE, Li J, Belfer I, Qin L. Integration of pain score and morphine consumption in analgesic clinical studies. J Pain. 2013;14(8):767-77.e8.
18. Silverman DG, O'Connor TZ, Brull SJ. Integrated Assessment of Pain Scores and Rescue Morphine Use During Studies of Analgesic Efficacy. Anesthesia & Analgesia. 1993;77(1).
19. Juul RV, Knøsgaard KR, Olesen AE, Pedersen KV, Kreilgaard M, Christrup LL, et al. A Model-Based Approach for Joint Analysis of Pain Intensity and Opioid Consumption in Postoperative Pain. Aaps j. 2016;18(4):1013-22.
20. Ristl R, Urach S, Rosenkranz G, Posch M. Methods for the analysis of multiple endpoints in small populations: A review. Journal of Biopharmaceutical Statistics. 2019;29(1):1-29.
21. Chen LH, Hedegaard H, author Warner M. Drug-poisoning deaths involving opioid analgesics: United States, 1999-2011: US Department of Health and Human Services, Centers for Disease Control and …; 2014.
22. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
23. Wang Q, Hu J, Cai L, Bahete A, Yang J, Kang P. Minimum Effective Concentration of Ropivacaine For Ultrasound-Guided Adductor Canal+ IPACK Block In Total Knee Arthroplasty. 2022.
24. Zhang Y, Liu L, Zheng L, Chen J, Huang L, Wang Q, et al. Comparison of effectiveness of ropivacaine infusion regimens for continuous femoral nerve block for recovery after total knee arthroplasty: a randomized double-blind trial. Journal of Pain Research. 2020;13:997.
25. Machi AT, Sztain JF, Kormylo NJ, Madison SJ, Abramson WB, Monahan AM, et al. Discharge readiness after tricompartment knee arthroplasty: adductor canal versus femoral continuous nerve blocks—a dual-center, randomized trial. Anesthesiology. 2015;123(2):444-56.
26. Nicolino TI, Costantini J, Carbó L. Complementary saphenous nerve block to intra-articular analgesia reduces pain after total knee arthroplasty: a prospective randomized controlled trial. The Journal of Arthroplasty. 2020;35(6):S168-S72.
27. Mont MA, Beaver WB, Dysart SH, Barrington JW, Del Gaizo DJ. Local infiltration analgesia with liposomal bupivacaine improves pain scores and reduces opioid use after total knee arthroplasty: results of a randomized controlled trial. The Journal of arthroplasty. 2018;33(1):90-6.
28. Rawal N, Viscusi E, Peloso PM, Minkowitz HS, Chen L, Shah S, et al. Evaluation of etoricoxib in patients undergoing total knee replacement surgery in a double-blind, randomized controlled trial. BMC musculoskeletal disorders. 2013;14(1):1-14.
29. Kim DH, Lin Y, Goytizolo EA, Kahn RL, Maalouf DB, Manohar A, et al. Adductor canal block versus femoral nerve block for total knee arthroplasty: a prospective, randomized, controlled trial. Anesthesiology. 2014;120(3):540-50.

30. YaDeau JT, Mayman DJ, Jules-Elysee KM, Lin Y, Padgett DE, DeMeo DA, et al. Effect of Duloxetine on Opioid Use and Pain After Total Knee Arthroplasty: A Triple-Blinded Randomized Controlled Trial. The Journal of Arthroplasty. 2022;37(6):S147-S54.
31. Farag E, Atim A, Ghosh R, Bauer M, Sreenivasalu T, Kot M, et al. Comparison of three techniques for ultrasound-guided femoral nerve catheter insertion: a randomized, blinded trial. Anesthesiology. 2014;121(2):239-48.
32. Altman DG, Royston P. The cost of dichotomising continuous variables. Bmj. 2006;332(7549):1080.
33. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106(3):337-45.
34. Wylde V, MacKichan F, Bruce J, Gooberman-Hill R. Assessment of chronic post-surgical pain after knee replacement: Development of a core outcome set. European Journal of Pain. 2015;19(5):611-20.
35. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.
36. Piccioni F, Doronzio A, Brambilla R, Melis M, Langer M. Integration of pain scores, morphine consumption and demand/delivery ratio to evaluate patient-controlled analgesia: the C-SIA score. Korean Journal of Anesthesiology. 2017;70(3):311-7.

APPENDIX ONE

Search Strategy using MEDLINE:

MEDLINE (OVID)
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
---

1 Arthroplasty, Replacement, Knee/ (30027)
2 Knee Joint/su [Surgery] (19447)
3 TKA.mp. (15033)
4 (knee adj3 (replace* or arthroplast*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (44402)
5 (knee* adj3 (replac* or arthroplast* or prosthe*)).mp. (48173)
6 exp Knee Joint/ (69469)
7 Knee/ (15721)
8 Arthroplasty, Replacement/ (6535)
9 (arthroplast* or replac* or prosthe*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (821407)
10 (6 or 7) and (8 or 9) (17603)
11 1 or 2 or 3 or 4 or 5 or 10 (62064)
12 randomized controlled trial.pt. (578719)
13 controlled clinical trial.pt. (95070)
14 randomi?ed.ab. (691152)
15 placebo.ab. (232376)
16 drug therapy.fs. (2536878)
17 randomly.ab. (392974)
18 trial.ab. (619576)
19 groups.ab. (2417902)
20 or/12-19 (5499055)
21 exp animals/ not humans.sh. (5053872)
22 20 not 21 (4793832)
23 11 and 22 (16367)
24 limit 23 to yr="2012 -Current" (11585)

CHAPTER 3: OPIOID REDUCTION AND ENHANCED RECOVERY IN ORTHOPAEDIC SURGERY (OREOS): A PROTOCOL FOR A FEASIBILITY RANDOMIZED CONTROLLED TRIAL IN KNEE REPLACEMENT PATIENTS

Opioid Reduction and Enhanced Recovery in Orthopaedic Surgery (OREOS): A Protocol for a Feasibility Randomized Controlled Trial in Knee Replacement Patients

OREOS Trial Investigators

Writing Committee: Kim Madden PhD[1,2,3], Sushmitha Pallapothu MSc(cand)[3], Darren Young Shing MD(cand)[4], Anthony Adili MD, PEng, FRCSC[1,2], Mohit Bhandari MD, PhD, FRCSC[1,3], Lisa Carlesso PT, PhD[5], Moin Khan MD, MSc, FRCSC[1,2], Ydo V. Kleinlugtenbelt MD, PhD[6], Adrijana Krsmanovic PhD, C.Psych[2,10], Matilda Nowakowski PhD C.Psych[2,10], Tara Packham PhD, OTReg[5], Eric Romeril ACPR, BSc.Pharm., RPh[7], Jean-Eric Tarride PhD[2,3,9], Lehana Thabane PhD[2,3], Daniel M Tushinski MD, MSc, FRCSC[1,7], Christine Wallace BScPhm, RPh,[2] Mitchell Winemaker MD, FRCSC[7], Harsha Shanthanna MD, PhD, FRCPC[1,2,8].

1. Department of Surgery, McMaster University
2. Research Institute of St. Joseph's Healthcare Hamilton
3. Department of Health Research Methods, McMaster University
4. University of Ottawa, Department of Medicine
5. School of Rehabilitation Science, McMaster University
6. Deventer Hospital, Department of Orthopaedics
7. Hamilton Health Sciences – Juravinski Hospital
8. Department of Anesthesia, McMaster University
9. Center for Health Economics and Policy Analyses, McMaster University
10. Department of Psychiatry and Behavioural Neurosciences, McMaster University

ABSTRACT

Background**:** Knee arthritis is a leading cause of limited function and long-term disability in older adults. Despite a technically successful total knee arthroplasty (TKA), around 20% of patients continue to have persisting pain with reduced function, and low quality of life. Many of them continue using opioids for pain control, which puts them at risk for potential long-term adverse effects such as dependence, overdose, and risk of falls. Although persisting pain and opioid use after TKA have been recognised to be important issues, individual strategies to decrease their burden have limitations and multi-component interventions, despite their potential, have not been well studied. In this study, we propose a multi-component pathway including personalized pain management, facilitated by a pain management coordinator. The objectives of this pilot trial are to evaluate feasibility (recruitment, retention, and adherence), along with opioid-free pain control at 8 weeks after TKA.

Methods: This is a protocol for a multicentre pilot randomized controlled trial using a 2-arm parallel group design. Participants in the intervention group will receive support from a pain management coordinator who will facilitate a multicomponent pain management pathway including: 1) preoperative education on pain and opioid use; 2) preoperative risk identification and mitigation; 3) personalized post-discharge analgesic prescriptions; 4) continued support for pain control and recovery up to 8 weeks post-op. Participants in the control group will undergo usual care. The primary outcomes of this pilot trial are to assess

the feasibility of participant recruitment, retention, and adherence to the interventions, and key secondary outcomes are persisting pain and opioid use.

Discussion: The results of this trial will inform implementation of a coordinated approach, integrating a multicomponent pain pathway to improve pain control and reduce harms, while keeping an emphasis on patient centered care and shared decision making.

Trial Registration: Prospectively registered in Clinicaltrials.gov (NCT04968132).

Keywords: Persisting pain, Feasibility, Opioid reduction, Knee arthroplasty, Multicomponent intervention

BACKGROUND

Arthritis is a very common and painful joint condition affecting 6 million Canadians, and nearly 1 in 2 Canadians over the age of 65 (1, 2). Osteoarthritis (OA) is the most common form, affecting more people than all other forms of arthritis combined (2). End-stage knee OA is treated by total knee replacement (also known as total knee arthroplasty; TKA), which results in substantial improvements in pain and functional outcomes for most people. TKA is the second most common surgery in Canada with >75,000 procedures performed in Canada in 2018-2019 (3, 4). Although TKA is considered to be a successful treatment, around 20-25% of patients have lasting pain after surgery (5, 6). Chronic post-surgical pain (CPSP) is complex, and factors known to be associated with it include pre-operative psychological factors like anxiety, depression, and pain catastrophizing; pre-existing chronic pain and opioid use; and the severity and duration of postoperative pain (7-10). Among patients who develop CPSP after TKA, 56% of them continue use of opioid analgesics at 30 days after surgery, 40% after 4 months, and 25% after 2 years (11-13). The traditional approach to post-discharge pain management has been for orthopaedic surgeons to prescribe a set number of institutionally standardized pain management medications, which can include non-steroidal anti-inflammatory drugs (NSAIDs) and/or opioids, without accounting for individual pain trajectories and preferences. However, studies have suggested that distinguishing problematic pain resolution from normal resolution may not be possible unless we appreciate individual patterns over time by personalized assessment and management following TKA (14).

Opioids are an important part of perioperative pain management (15-17). However, their potential for long-term adverse effects such as persistent opioid use (POU) (18), addiction and dependence, overdose, diversion of unused pills (19, 20), and death in severe cases are well recognized (15, 21). Patients using preoperative opioids are particularly at risk; 64 to 77% of chronic opioid users continue to use opioids after surgery, particularly after arthroplasty (22, 23). In general, reducing opioid prescriptions can certainly help as not all patients may need opioids (24-26). However, limiting opioids without individualizing the treatment of persistent pain can potentially drive patients to illicit sources.

A recent scoping review identified 141 studies to decrease opioid use in orthopedic surgery, of which 70 were in the arthroplasty field (49.6%). Only 8.5% (12/141) of studies followed patients beyond seven days, only four had follow up of three or more months, further only 24% of TKA studies used multimodal interventions. None of them had a preoperative education and risk reduction component. Important findings included were: 1) Both preoperative pain and preoperative opioids independently increase the risk of persistent pain and chronic opioid needs (10, 22, 27-19). Despite this, most studies have excluded such patients, thereby limiting the external validity (30); 2) most studies are associated with attempts to achieve in-hospital opioid free care (31, 32), which has not been shown to influence long term opioid use (17); 3) most studies have focused on single interventions with limited or no effect (33, 34), 4) the majority of studies involve a follow-up duration of a few weeks or less (30, 31, 34); and most importantly, 5) existing trials do not take into account the individual variability within patients for pain resolution (35).

Perioperative surgical home (PSH) care pathways are defined by the American Society of Anesthesiologists as "patient-centered and physician-led multidisciplinary and team-based system of coordinated care that guides the patient throughout the entire surgical experience". Over the last decade or so, several publications have highlighted its potential role in overcoming problems at the population level by providing a system that provides coordination during all phases of surgery (36). Despite this, a recent (2020) systematic review on PSH demonstrated only low evidence for studies supporting its use (37). Similarly, there are no RCTs on transitional pain clinic approaches, which have become conceptually very popular and are currently being used in many centres (38). Based on the literature, we identified the need of four components that form the core of our care pathway/intervention arm; 1) patient education and expectation setting, 2) identification and modification of preoperative risk factors, 3) personalized analgesic prescriptions, and 4) continued support for pain control and recovery**.**

In our study, we will employ a pain management coordinator to coordinate all aspects of the trial intervention. Patients will be taken through a multicomponent pathway during their perioperative phases, which will be compared with routine care. Pain management coordinators have been used in many such models of care, such as for osteoporotic fracture screening and prevention (39), pre-habilitation for frail surgical patients (40), and delirium prevention in surgical patients (41).

Before embarking on a larger trial, we plan to assess the feasibility of implementing the components at each site. The overarching goal is to implement and evaluate a

coordinated approach to clinical care, to improve pain control and reduce harms, with an emphasis on patient centred care and shared decision making.

OBJECTIVES

The principal objective is to assess the feasibility of conducting a larger randomized controlled trial (RCT) of a multicomponent care pathway versus standard care to improve pain control and decrease opioid use in TKA patients.

Feasibility objectives

The feasibility objectives will be to evaluate adherence to the study intervention, participant recruitment, and participant retention. We will observe any challenges in implementing the study interventions and data collection procedures to consider appropriate changes to the final design.

Clinical objectives

The clinical objectives will be the objectives of the definitive trial. The primary objective for the definitive trial will be to assess the effect of the multicomponent interventional pathway on opioid free pain control at 8 weeks after TKA versus standard care. We define opioid free pain control as a state of good pain control (three consecutive days of <4/10 pain score on a 0-10 numerical rating scale [NRS] with no opioid use for the operated knee). Other objectives include evaluating:

- Presence of CPSP at 3, 6, 9, and 12 months (46)

- Presence of POU at 3, 6, 9, and 12 months
- Average intensity of CPSP at rest and with movement at 3, 6, 9, and 12 months
- Satisfaction with pain control at 3, 6, 9, and 12 months
- Return to function at 3, 6, 9, and 12 months
- Knee function at 3, 6, 9, and 12 months
- Quality of life at 3, 6, 9, and 12 months
- Operative and knee-related complications during the study
- Economic analyses

METHODS

Overview of the design

This is a multicenter pilot randomized controlled trial using a 2-arm parallel group design (Figure 1). For the pilot trial, we aim to recruit participants from three high volume arthroplasty hospitals in Ontario. For the definitive trial, we will aim to increase this to 7-10 sites across Canada.

Patient selection

All patients who are being scheduled for primary elective TKA will be screened for eligibility by participating surgeons (target approximately 1-6 weeks before surgery). We will aim to include proportions of men and women in our trial that are representative of the TKA population. We will record numbers of ineligible patients and those who decline to participate. The surgeon or their delegate will inform potentially eligible patients by phone

or in person to invite them to speak with the research coordinator about the trial. Each institution will determine their own recruitment processes based on local research ethics board (REB)-approved practices. Sites will be allowed to select an informed consent method that meets their REB and local institutional guidelines. This could include written informed consent or verbal consent. The informed consent process will be documented in all cases.

Eligibility criteria

Inclusion criteria:

- Adult (18+)
- Undergoing elective TKA for knee arthritis
- Can use a simple electronic device (phone or tablet)
- Provide informed consent to participate

Exclusion criteria:

- Revision surgery
- Simultaneous bilateral arthroplasties
- Unable to consent (e.g., cognitive disability or substantial language barrier without a support person)

Interventions

<u>Intervention group</u>

Participants will participate in a multicomponent pathway coordinated by a trained pain management coordinator who will facilitate patient participation and engagement with each interventional component. Study interventions will start 1-6 weeks before their surgery. In the intervention group, patients will participate in study interventions through their preoperative, in-hospital, and post-operative period, up to two months after their surgery.

The pain management coordinator will facilitate delivery of preoperative components of pain education, screening patients for high-risk of opioid use, depression, anxiety and/or kinesiophobia, and cognitive behavioural skill (CBS) sessions for high-risk patients (based on cognitive behavioural therapy [CBT] principles); and post-operatively, the coordinator will facilitate personalized analgesic prescriptions, and check in with patients about pain control and functional recovery. This role can be fulfilled by any health care personnel who can be trained to deliver patient education and conduct CBS sessions (e.g., medical graduate, allied health professional). All intervention components will be standardized and protocolized in an intervention manual. Study outcomes will be collected by separate research personnel not involved in the patient's clinical care.

Pre-operatively, participants will view pre-recorded online presentations on 'understanding pain after surgery' and 'managing pain after surgery' developed by a pain physician in collaboration with a psychologist, occupational therapist, and physiotherapist. Educational content includes simple pain physiology, surgical pain experience and resolution, setting expectations, goals of functional pain relief, managing daily activities,

and opioid benefits and risks. The coordinator will facilitate and encourage participants' access to these online modules and will answer participants' questions.

The pain management coordinator will conduct preoperative risk assessments based on preoperative opioid usage, depression, anxiety, and kinesiophobia. Participants who meet one or more of the high-risk criteria will be asked to complete two sessions of CBS sessions and suggestions on opioid sparing strategies (in-person or virtual) (7, 28, 42). Preoperative opioid use increases the risk of poor outcomes. If the participant is considered high risk for opioid use and is willing to reduce their opioid use, the pain management coordinator will work with the site pain physician to safely reduce their opioid use. Very few opioid reduction studies focus on high-risk populations, so the evidence behind identification of individual risk components and preoperative risk education is lacking. However, this strategy is recommended by the American Society of Enhanced Recovery (28).

Post-discharge, patients will have scheduled virtual/telephone check-ins with the pain management coordinator before hospital discharge and at 1, 2, 3, 4, 6, and 8 weeks after surgery (total 7 check-ins). During these meetings, the coordinator will deliver continued support for pain control and recovery, and personalized analgesic prescriptions. The pain management coordinator will encourage the use of non-opioid analgesics and non-pharmacological measures (e.g., exercise, mindfulness, ice) (43) and encourage safe use of opioids where appropriate. The coordinator will also answer questions and facilitate virtual or in-person meetings with the surgical team if problems arise. Patients who are willing to reduce their opioid use will be supported to slowly wean their opioids, with the support of

a pain physician. Based on a study assessing guided opioid tapering support, patients were able to successfully reduce/discontinue their opioid consumption following TKA (44). Therefore, we believe that many patients will be enthusiastic about post-operative opioid tapering and discontinuation if their knee pain has been controlled by TKA.

The pain management coordinator will facilitate individualized discharge prescriptions integrating patient preferences. For example, some patients prefer not to use opioids because they have experienced adverse effects in the past, while others feel that opioids work well for them. Some patients would like to try non-pharmacological pain management strategies such as exercise or cold therapy.

Control Group

All patients will receive usual care at their center. Presently, this does not include a pain management coordinator. Existing pre-operative knee classes, at enrolling sites, are not typically oriented towards pain education and appropriate opioid use. Post-operative discharge medications vary according to surgeon's preference and are not typically individualized to patients' needs. The research personnel will follow all participants for study outcomes.

Perioperative Care and Surgical Treatment

Participants will undergo usual perioperative and surgical care at their centre. Choice of surgical technique, anesthetic technique, and in-hospital analgesia will be left to the treating surgeon, anesthesiologist, and allied health team. Individual analgesic

components in-hospital have not been shown to influence post-discharge outcomes such as POU or CPSP in larger studies (17).

Study Outcomes

Primary (Feasibility) Outcomes and Criteria for Success

Feasibility outcomes include intervention adherence, participant recruitment, and participant retention (Table 1). We will note the percentage of participants receiving at least 3 of the 4 trial intervention components. We will consider >90% as feasible; 80-90% to consider design modifications; and 80% as not feasible. This will be captured using an adherence checklist by the coordinator. We aim to recruit 100 patients in 4 months. We will consider >90% participant retention to be feasible at 12 months post-operatively, 80-90% to consider design modifications, and <80% is not feasible.

Secondary (Clinical) Outcomes

The following will be the outcomes for our definitive trial. Pain control and opioid analgesics are interlinked outcomes (45). Recent studies have highlighted the need to consider both opioid use and pain control as patient-important, and the need to evaluate pain and opioid use trajectories (46, 47). Hence, our primary outcome will be to assess the effect of the multicomponent pain management pathway on "opioid free pain control" at 8 weeks after TKA; defined as three or more consecutive days of <4/10 pain score on a 0-10 NRS with no opioid use for the operated knee. Secondary outcomes will include presence of CPSP; intensity of resting and movement evoked pain; POU; satisfaction with pain

control; quality of life, and complication rates. These outcomes will be collected at 3, 6, 9, and 12 months. To inform the future health economic evaluation of the main trial we will also capture information on the costs of providing the intervention, healthcare resource use, and productivity at 3, 6, 9, and 12 months post-operatively.

Measurement of Clinical Outcomes and Economic

Opioid Free Pain Control: For both groups, we will use a daily electronic diary to capture pain scores and opioid use between 1-6 weeks pre-op (to familiarize the patient on the use of the diary) and 8 weeks post-op. We will identify the number of patients achieving opioid-free pain control (defined in previous paragraph) in the intervention and control groups. We have partnered with ManagingLife Inc., who will provide the ManageMyPain app to capture daily pain scores and opioid use. This application is easy to use and secure. It is both Health Insurance Portability and Accountability (HIPPA) and Personal Information Protection and Electronic Documents Act (PIPEDA) compliant and has been recognized by Ontario Health Network (OTN) as an approved platform. This app has been used in previous studies to track pain resolution in surgical patients. Our surgeons estimate that 75% of their patients have a smartphone. For the approximately 25% who do not, we have access to donated smartphones to be used for research purposes. Alternatively in patients who cannot use MMP, a paper diary will be used.

We will measure the presence of CPSP as defined as per the International Classification of Diseases version-11 (ICD-11) (48).

We will measure CPSP Pain Intensity at Rest and during Movement using the 0-10 Numerical Rating Scale (NRS).

We will measure Persistent Opioid Use (POU) as a binary outcome as defined as the presence of daily opioid use, started after surgery, or increased after surgery.

Using a 0 to 100 scale (0=extremely dissatisfied, 100=extremely satisfied), we will measure satisfaction with pain control.

We will assess return to function using the 5-item Return to Work questionnaire to assess the ability to return to work, home, and leisure activities.

Using the 12-item Oxford Knee Score, we will assess improvement in knee function and pain following total knee replacement (49).

We will assess health-related quality of life using the Euro-QoL 5 Dimensions instrument consisting of 5 dimensions, including mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression, which contains five levels of answers per dimension (50).

We will collect intervention costs and healthcare resource utilization information (e.g., hospitalization, physician visits) as well as information on productivity (e.g., time missed

from work) using a self-administered questionnaire, which we developed for the purpose of this study based on our previous work (51).

We will also collect any surgery-related and knee-related adverse events, pain medication related adverse events, readmissions, and serious adverse events (SAEs).

Randomization

The unit of randomization will be individual participants. We will use a 1:1 allocation ratio, stratified by site, with random block sizes of 2 and 4. Randomization will be completed 1-6 weeks before surgery to allow time for the pre-operative education interventions. We will use a centralized online randomization system integrated into REDCap to ensure allocation concealment. A statistician not otherwise associated with the trial will generate the randomization sequence.

Study Follow-Up

Participants will be followed from the time of their study inclusion (1-6 weeks pre-surgery) to 12 months after surgery. We will collect baseline data before surgery. We will collect daily pain scores using an electronic diary up to 8 weeks after surgery, and we will collect post-operative outcomes at 3, 6, 9, and 12 months after surgery (Table 2).

Protecting Against Sources of Bias

<u>Blinding</u>

Due to the nature of the study interventions, participants and the health care team cannot be blinded. We will have an independent blinded surgeon to evaluate each adverse event to minimize the risk of bias for that outcome. The primary study outcome of non-opioid pain control will be collected using a daily e-diary up to 8 weeks. Other study outcomes will be collected by research personnel not involved in the participants' clinical care. Data analysts will be blinded for all outcomes.

Minimizing Contamination and Co-Interventions

Since the existing standard of care does not involve the coordinator or any component of interventions, there is minimal risk of contamination. Patients are allowed to receive other interventions outside of the study, but the role of a pain management coordinator currently does not exist outside of our study. Alternatively, there is a risk if patients are randomized to intervention but do not ultimately receive it. To minimize the risk of crossover, all efforts will be taken to maintain communication between the research personnel and the pain management coordinator. We will also hold weekly team meetings to provide updates on all patients. Participants who are receiving two joint replacements during the study period will only be included for one of their surgeries.

Minimizing Expertise Bias

The CBS sessions are based on the principles of CBT. Although no formal CBT training is required, we will employ pain management coordinators with some prior patient contact experience within the healthcare setting, and we will also develop a pain CBS

"bootcamp" to ensure pain management coordinators can successfully implement the CBS sessions, along with training for safe opioid weaning. We also have a pain psychologist within the study team to resolve any challenges relating to CBS sessions for specific participants.

Components of the intervention such as personalized prescriptions, pain management, and support may also present expertise bias, as the pain management coordinator will be the participant's first point of contact for all components. Therefore, to maintain consistency among sites, we will also engage the lead pain physician to liaise with each site to support the pain management coordinator in any decisions regarding pain management and prescriptions.

Minimizing Attrition Bias

Once a participant is enrolled in the trial, every reasonable effort will be made to follow the participant for the entire duration of the study period (12 months). Previously established orthopaedic-specific procedures developed and refined at our central coordination and methods centre will be implemented to improve participant retention. Our research group has consistently used and improved our participant retention strategies over the past 15 years and has published papers on minimizing loss to follow-up in orthopaedic trials (52). In our group's four most recent large trials, the loss to follow-up percentages were: A-PREP trial – 4% (53), HEALTH trial –14.9% (54), FLOW trial –10% (55), FAITH trial - 9% (56). Key strategies used to minimize loss to follow-up: aligning the follow up with standard of care visits; collecting more than one piece of contact information for the

participant; research personnel will verify participants' contact information at each visit and ask the participants their preferred form of contact; prioritizing outcomes if there is participant burden; and requesting permission to access medical records.

Statistical Methods

Sample Size Determination

This pilot trial is not powered to detect clinical differences, so we based our sample size on pilot trial sample size calculations using a confidence interval approach suggested by Thabane et al (56). We believe the study will be feasible if participant retention is 90% or greater and will consider >80% retention acceptable with modifications. If 90/100 participants adhere to the study intervention, then the lower bound of the confidence interval will exclude 80% and we will consider the trial feasible. Therefore, we will include 100 participants in this pilot trial.

Primary Analysis

Feasibility outcomes will be reported descriptively as numbers and percentages with 95% confidence intervals (CI). This pilot trial will not be powered to detect differences in clinical outcomes. Instead, we will report all clinical outcomes descriptively as point estimates and 95% CI, with minimally important differences presented for context, where available. We will also report hazard ratios for our primary outcome and time-to-event data graphically using a Kaplan-Meier survival curve. We will not impute for missing data in

the pilot trial. All analyses will be conducted as intention-to-treat. We will prepare a full statistical analysis plan (SAP) for the definitive trial analysis.

Interim Analysis

For this pilot trial, data will be analyzed only after completion of data collection. Interim analysis will be considered for the definitive trial.

Subgroup and Other Analyses

Subgroup and other analyses will only be considered for the definitive trial.

Economic Analyses

To assist with the future economic evaluation of the definitive trial we will collect information on costs (e.g., intervention costs, costs related to healthcare resource utilization and productivity) and quality of life. Healthcare resource utilization (e.g., hospitalization, emergency department visits, physician visits) and productivity (e.g., time missed from work) will be collected at baseline and at 3, 6, 9, and 12 months using a short economic questionnaire. The time recall will be 3 months (e.g., over the last 3 months, have you been hospitalized?). Healthcare resource utilization and productivity will be costed using publicly available unit costs from Ontario (e.g., Ontario Schedule of Benefits) or from the Canadian Institute for Health Information (e.g., hospitalization costs). Health-related quality of lie will be collected at baseline and at 6 and 12 months using the Euro-Qol 5 Dimensions-5L (EQ-5D-5L), which is a well-validated and widely used quality of life

instrument that can assess health utilities for the purpose of health economic analyses. Using the Canadian algorithm of the EQ-5D-5L (57), the health utility scores derived from the EQ-5D-5L questionnaire will be weighted by time spent in health states using an area-under-the-curve approach to calculate QALYs. We will also request participants consent for potential data linkage with Institute for Clinical Evaluative Sciences (ICES) administrative data. Since this is a pilot trial, costs and QALYs associated with each study arm will be reported as point estimates along with confidence intervals but not compared in a formal economic evaluation. The analyses will be conducted from the payer (e.g., Ministry of Health) and societal perspectives.

Data Monitoring

Steering Committee

Our co-investigators make up the Steering Committee for the trial. Steering Committee members are an interdisciplinary group of experts in key fields including anesthesia/ pain management, orthopaedic surgery, health economics, biostatistics, psychology, pharmacy, occupational therapy, physiotherapy, and clinical trials methodology. The Steering Committee will be chaired by the PI and will be responsible for advising on key clinical and methodological issues at all stages of the trial. For the pilot trial, we do not plan to have a formal Data & Safety Monitoring Committee (DSMC) because all interventions are standard care and are not expected to pose greater risk than the control group arm.

Trial Coordination

The Surgical Methods Center (SMC), McMaster University will be the trial Methods Centre and will be responsible for coordinating the day-to-day operations of the trial. The CEO has conducted some of the largest multinational trials and observational studies in orthopaedics, including the PREPARE and A-PREP trials (n=8,000), FLOW trial (n=2551), the PRAISE study (n=2945) and the INORMUS study (n=30,000). The CEO has the infrastructure to successfully conduct large trials including research coordinators, data managers, statisticians, a network of investigators, and required office space.

Harms

For this pilot trial we will collect all knee and surgery-specific AEs, AEs associated with the use of pain medications, readmissions, and serious adverse events (SAEs). We do not anticipate many risks to study participants beyond usual care. We provide education about safe opioid use and disposal and recognize the potential for opioid withdrawal if opioids are tapered too rapidly. Postoperative prescriptions will be structured and any reduction to chronic opioid use will be monitored, and our pain physicians will develop a structured set of operating procedures to minimize this risk, both preoperatively and postoperatively. Most importantly, the approach throughout the trial will be one of participant engagement and shared decision making.

Ethical considerations

This study will be conducted according to international standard of ICH-GCP, applicable government regulations, and institutional research policies and procedures. We will require ethics approval from each site's local REB prior to initiating this trial protocol.

Dissemination Policy

While emphasizing the core concepts and delivery involved in the preoperative and postoperative components, our interventional pathway is designed to be adaptable to individual centres. The pre-operative education component will be made available online free of charge. The intervention can also be easily adaptable to other surgical fields. We will partner with the Canadian Orthopaedic Association (COA) and Canadian Anesthesiologists Society (CAS) to help disseminate our study information to orthopaedic surgeons and anesthesiologists in Canada, plus international members. We will also partner with our university and hospital press offices to distribute a press release for the general public.

Declarations

Ethics approval and consent to participate

We received ethics approval from the Hamilton Integrated Research Ethics Board (Project #13828). Each additional clinical site will obtain local ethics approval before beginning the study. Participants will provide written informed consent before participating.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study is funded by The Research Institute of St. Joseph's Hamilton; McMaster Surgical Associates; Michael DeGroote Institute for Pain Research and Care; Canadian Anesthesiologists' Society; & the Canadian Orthopaedic Foundation. The funding sources had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Author's contributions

HS and KM are Co-PIs and conceived the study design and oversee its conduct. SP drafted the manuscript and all writing committee members contributed substantially to revising the drafts. All writing committee members read and approved the final manuscript.

Acknowledgements

The OREOS Investigators (writing committee) are Kim Madden (co-chair), Sushmitha Pallapothu (project officer), Darren Young Shing, Anthony Adili, Mohit Bhandari, Lisa Carlesso, Moin Khan, Ydo V. Kleinlugtenbelt, Adrijana Krsmanovic, Matilda Nowakowski, Tara Packham, Eric Romeril, Jean-Eric Tarride, Lehana Thabane, Daniel M Tushinski, Christine Wallace, Mitchell Winemaker, Harsha Shanthanna (co-chair).

Enrolling sites:

St. Joseph's Healthcare Hamilton: Harsha Shanthanna, Kim Madden, Anthony Adili, Vickas Khanna, Sushmitha Pallapothu, Sidra Shoaib, Kim Irish, Nathasha Rajapaksege, Japneet Sachdeva, Darren Young Shing, Annie George, Sophia Mangala

Hamilton Health Sciences – Juravinski Hospital: Daniel M Tushinski, Thomas J Wood, Kamal Bali, Elaheh Adly, Laura Puri, Isabelle Tate, Yasaman Amini

Oakville Trafalgar Memorial Hospital: Paul Zalzal, Heather Brien, Balaji Balasubramaniam, Adic Perez, Surbhi Handa

REFERENCES:

1. Government of Canada SC. Arthritis, by age group [Internet]. 2017 [cited 2022 Dec 14]. Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310009606
2. The Truth About Arthritis - Prevalence & Impact [Internet]. [cited 2022 Dec 14]. Available from: https://arthritis.ca/about-arthritis/what-is-arthritis/the-truth-about-arthritis
3. Inpatient Hospitalizations, Surgeries, Newborns and Childbirth Indicators, 2016–2017 — CIHI Snapshot.
4. CJRR annual report: Hip and knee replacements in Canada | CIHI [Internet]. [cited 2022 Dec 14]. Available from: https://www.cihi.ca/en/cjrr-annual-report-hip-and-knee-replacements-in-canada
5. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open. 2012 Jan 1;2(1):e000435.
6. Bourne RB, Chesworth BM, Davis AM, Mahomed NN, Charron KDJ. Patient Satisfaction after Total Knee Arthroplasty: Who is Satisfied and Who is Not? Clin Orthop Relat Res. 2010 Jan;468(1):57–63.
7. Rice DA, Kluger MT, McNair PJ, Lewis GN, Somogyi AA, Borotkanics R, et al. Persistent postoperative pain after total knee arthroplasty: a prospective cohort study of potential risk factors. Br J Anaesth. 2018 Oct 1;121(4):804–12.
8. Correll D. Chronic postoperative pain: recent findings in understanding and management [Internet]. F1000Research; 2017 [cited 2022 Dec 14]. Available from: https://f1000research.com/articles/6-1054
9. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. The Lancet. 2019 Apr 13;393(10180):1537–46.
10. Smith SR, Bido J, Collins JE, Yang H, Katz JN, Losina E. Impact of Preoperative Opioid Use on Total Knee Arthroplasty Outcomes. JBJS. 2017 May 17;99(10):803–8.
11. Grosu I, Lavand'homme P, Thienpont E. Pain after knee arthroplasty: an unresolved issue. Knee Surg Sports Traumatol Arthrosc. 2014 Aug 1;22(8):1744–58.
12. Buvanendran A, Valle CJD, Kroin JS, Shah M, Moric M, Tuman KJ, et al. Acute postoperative pain is an independent predictor of chronic postsurgical pain following total knee arthroplasty at 6 months: a prospective cohort study. Reg Anesth Pain Med [Internet]. 2019 Mar 1 [cited 2022 Dec 14];44(3). Available from: https://rapm.bmj.com/content/44/3/e100036
13. Andersen LØ, Gaarn-Larsen L, Kristensen BB, Husted H, Otte KS, Kehlet H. Subacute pain and function after fast-track hip and knee arthroplasty. Anaesthesia. 2009 May;64(5):508–13.
14. Shechter R, Speed TJ, Blume E, Singh S, Williams K, Koch CG, et al. Addressing the Opioid Crisis One Surgical Patient at a Time: Outcomes of a Novel Perioperative Pain Program. Am J Med Qual. 2020 Jan 1;35(1):5–15.
15. Alexander JC, Patel B, Joshi GP. Perioperative use of opioids: Current controversies and concerns. Best Pract Res Clin Anaesthesiol. 2019 Sep 1;33(3):341–51.

16. Egan TD. Are opioids indispensable for general anaesthesia? Br J Anaesth. 2019 Jun 1;122(6):e127–35.
17. Shanthanna H, Ladha KS, Kehlet H, Joshi GP. Perioperative Opioid Administration: A Critical Review of Opioid-free versus Opioid-sparing Approaches. Anesthesiology. 2021 Apr 1;134(4):645–59.
18. Jivraj NK, Raghavji F, Bethell J, Wijeysundera DN, Ladha KS, Bateman BT, et al. Persistent Postoperative Opioid Use: A Systematic Literature Search of Definitions and Population-based Cohort Study. Anesthesiology. 2020 Jun 1;132(6):1528–39.
19. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med. 2016 Sep 1;176(9):1286–93.
20. Rudd RA. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep [Internet]. 2016 [cited 2022 Dec 14];65. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm655051e1.htm
21. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: A systematic review. J Pain. 2002 Jun 1;3(3):159–80.
22. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic. Anesth Analg. 2017 Nov;125(5):1733–40.
23. Zarling BJ, Yokhana SS, Herzog DT, Markel DC. Preoperative and Postoperative Opiate Use by the Arthroplasty Patient. J Arthroplasty. 2016 Oct 1;31(10):2081–4.
24. Fujii MH, Hodges AC, Russell RL, Roensch K, Beynnon B, Ahern TP, et al. Post-Discharge Opioid Prescribing and Use after Common Surgical Procedure. J Am Coll Surg. 2018 Jun;226(6):1004–12.
25. Thiels CA, Ubl DS, Yost KJ, Dowdy SC, Mabry TM, Gazelka HM, et al. Results of a Prospective, Multicenter Initiative Aimed at Developing Opioid-prescribing Guidelines After Surgery. Ann Surg. 2018 Sep;268(3):457–68.
26. Hannon CP, Calkins TE, Li J, Culvern C, Darrith B, Nam D, et al. The James A. Rand Young Investigator's Award: Large Opioid Prescriptions Are Unnecessary After Total Joint Arthroplasty: A Randomized Controlled Trial. J Arthroplasty. 2019 Jul 1;34(7):S4–10.
27. Cook DJ, Kaskovich SW, Pirkle SC, Mica MAC, Shi LL, Lee MJ. Benchmarks of Duration and Magnitude of Opioid Consumption After Total Hip and Knee Arthroplasty: A Database Analysis of 69,368 Patients. J Arthroplasty. 2019 Apr 1;34(4):638-644.e1.
28. Edwards DA, Hedrick TL, Jayaram J, Argoff C, Gulur P, Holubar SD, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Perioperative Management of Patients on Preoperative Opioid Therapy. Anesth Analg. 2019 Aug;129(2):553–66.
29. Reid DBC, Shah KN, Shapiro BH, Ruddell JH, Akelman E, Daniels AH. Mandatory Prescription Limits and Opioid Utilization Following Orthopaedic Surgery. JBJS. 2019 May 15;101(10):e43.
30. Sabesan VJ, Chatha K, Koen S, Dawoud M, Gilot G. Innovative patient education and pain management protocols to achieve opioid-free shoulder arthroplasty. JSES Int. 2020 May 4;4(2):362–5.

31. Fiore JF, Olleik G, El-Kefraoui C, Verdolin B, Kouyoumdjian A, Alldrit A, et al. Preventing opioid prescription after major surgery: a scoping review of opioid-free analgesia. Br J Anaesth. 2019 Nov 1;123(5):627–36.
32. Gormley J, Gouveia K, Sakha S, Stewart V, Emmanuel U, Shehata M, et al. Reduction of opioid use after orthopedic surgery: a scoping review. Can J Surg. 2022 Oct 20;65(5):E695–715.
33. Tedesco D, Gori D, Desai KR, Asch S, Carroll IR, Curtin C, et al. Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty: A Systematic Review and Meta-analysis. JAMA Surg. 2017 Oct 18;152(10):e172872.
34. Talboys R, Mak M, Modi N, Fanous N, Cutts S. Enhanced recovery programme reduces opiate consumption in hip hemiarthroplasty. Eur J Orthop Surg Traumatol. 2016 Feb 1;26(2):177–81.
35. Pagé MG, Katz J, Romero Escobar EM, Lutzky-Cohen N, Curtis K, Fuss S, et al. Distinguishing problematic from nonproblematic postsurgical pain: a pain trajectory analysis after total knee arthroplasty. PAIN. 2015 Mar;156(3):460–8.
36. Vetter TR, Kain ZN. Role of the Perioperative Surgical Home in Optimizing the Perioperative Use of Opioids. Anesth Analg. 2017 Nov;125(5):1653–7.
37. Cline KM, Clement V, Rock-Klotz J, Kash BA, Steel C, Miller TR. Improving the cost, quality, and safety of perioperative care: A systematic review of the literature on implementation of the perioperative surgical home. J Clin Anesth. 2020 Aug 1;63:109760.
38. Admiraal M, Hermanns H, Hermanides J, Wensing CGCL, Meinsma SL, Wartenberg HCH, et al. Study protocol for the TRUSt trial: a pragmatic randomised controlled trial comparing the standard of care with a transitional pain service for patients at risk of chronic postsurgical pain undergoing surgery. BMJ Open. 2021 Aug 1;11(8):e049676.
39. Beaton DE, Vidmar M, Pitzul KB, Sujic R, Rotondi NK, Bogoch ER, et al. Addition of a fracture risk assessment to a coordinator's role improved treatment rates within 6 months of screening in a fragility fracture screening program. Osteoporos Int. 2017 Mar 1;28(3):863–9.
40. Mello MT, Azocar RJ, Lewis MC. Geriatrics and the Perioperative Surgical Home. Anesthesiol Clin. 2015 Sep 1;33(3):439–45.
41. Janssen TL, Mosk CA, van Hoof-de Lepper CCHA, Wielders D, Seerden TCJ, Steyerberg EW, et al. A multicomponent prehabilitation pathway to reduce the incidence of delirium in elderly patients in need of major abdominal surgery: study protocol for a before-and-after study. BMC Geriatr. 2019 Mar 20;19(1):87.
42. Cai L, Gao H, Xu H, Wang Y, Lyu P, Liu Y. Does a program based on cognitive behavioral therapy affect kinesiophobia in patients following total knee arthroplasty? A randomized, controlled trial with a 6-month follow-up. The Journal of arthroplasty. 2018 Mar 1;33(3):704-10.
43. Joshi GP, Kehlet H. Postoperative pain management in the era of ERAS: An overview. *Best practice & research Clinical anaesthesiology* 2019;33(3):259-67. doi: 10.1016/j.bpa.2019.07.016
44. Hah JM, Trafton JA, Narasimhan B, Krishnamurthy P, Hilmoe H, Sharifzadeh Y, Huddleston JI, Amanatullah D, Maloney WJ, Goodman S, Carroll I. Efficacy of

motivational-interviewing and guided opioid tapering support for patients undergoing orthopedic surgery (MI-Opioid Taper): A prospective, assessor-blind, randomized controlled pilot trial. EClinicalMedicine. 2020 Nov 1;28:100596.
45. Gilron I, Carr DB, Desjardins PJ, Kehlet H. Current methods and challenges for acute pain clinical trials. Pain Rep. 2018 Apr 2;4(3):e647.
46. Carroll IR, Hah JM, Barelka PL, Wang CKM, Wang BM, Gillespie MJ, et al. Pain Duration and Resolution following Surgery: An Inception Cohort Study. Pain Med. 2015 Dec 1;16(12):2386–96.
47. Hah J, Mackey SC, Schmidt P, McCue R, Humphreys K, Trafton J, et al. Effect of Perioperative Gabapentin on Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort: A Randomized Clinical Trial. JAMA Surg. 2018 Apr 1;153(4):303–12.
48. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. PAIN. 2019 Jan;160(1):45–52.
49. The Oxford Knee Score [Internet]. Oxford University Innovation. [cited 2022 Dec 14]. Available from: https://innovation.ox.ac.uk/outcome-measures/oxford-knee-score-oks/
50. Ray GS, Ekelund P, Nemes S, Rolfson O, Mohaddes M. Changes in health-related quality of life are associated with patient satisfaction following total hip replacement: an analysis of 69,083 patients in the Swedish Hip Arthroplasty Register. Acta Orthop. 2019 Nov 4;91(1):48–52.
51. Tarride JE, Hopkins RB, Blackhouse G, Burke N, Bhandari M, Johal H, et al. Low-intensity pulsed ultrasound for treatment of tibial fractures. Bone Jt J. 2017 Nov;99-B(11):1526–32.
52. Madden K, Scott T, McKay P, Petrisor BA, Jeray KJ, Tanner SL, et al. Predicting and Preventing Loss to Follow-up of Adult Trauma Patients in Randomized Controlled Trials: An Example from the FLOW Trial. JBJS. 2017 Jul 5;99(13):1086–92.
53. PREP-IT Investigators. Aqueous skin antisepsis before surgical fixation of open fractures (Aqueous-PREP): a multiple-period, cluster-randomised, crossover trial. The Lancet. 2022 Oct 15;400(10360):1334-44.
54. Total Hip Arthroplasty or Hemiarthroplasty for Hip Fracture. N Engl J Med. 2019 Dec 5;381(23):2199–208.
55. A Trial of Wound Irrigation in the Initial Management of Open Fracture Wounds. N Engl J Med. 2015 Dec 31;373(27):2629–41.
56. Nauth A, Creek AT, Zellar A, Lawendy AR, Dowrick A, Gupta A, et al. Fracture fixation in the operative management of hip fractures (FAITH): an international, multicentre, randomised controlled trial. The Lancet. 2017 Apr 15;389(10078):1519–27.
57. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010 Jan 6;10(1):1.
58. Xie F, Pullenayegum E, Gaebel K, Bansback N, Bryan S, Ohinmaa A, et al. A Time Trade-off-derived Value Set of the EQ-5D-5L for Canada. Med Care. 2016 Jan;54(1):98–105.

Figure 1: OREOS Interventional Pathway

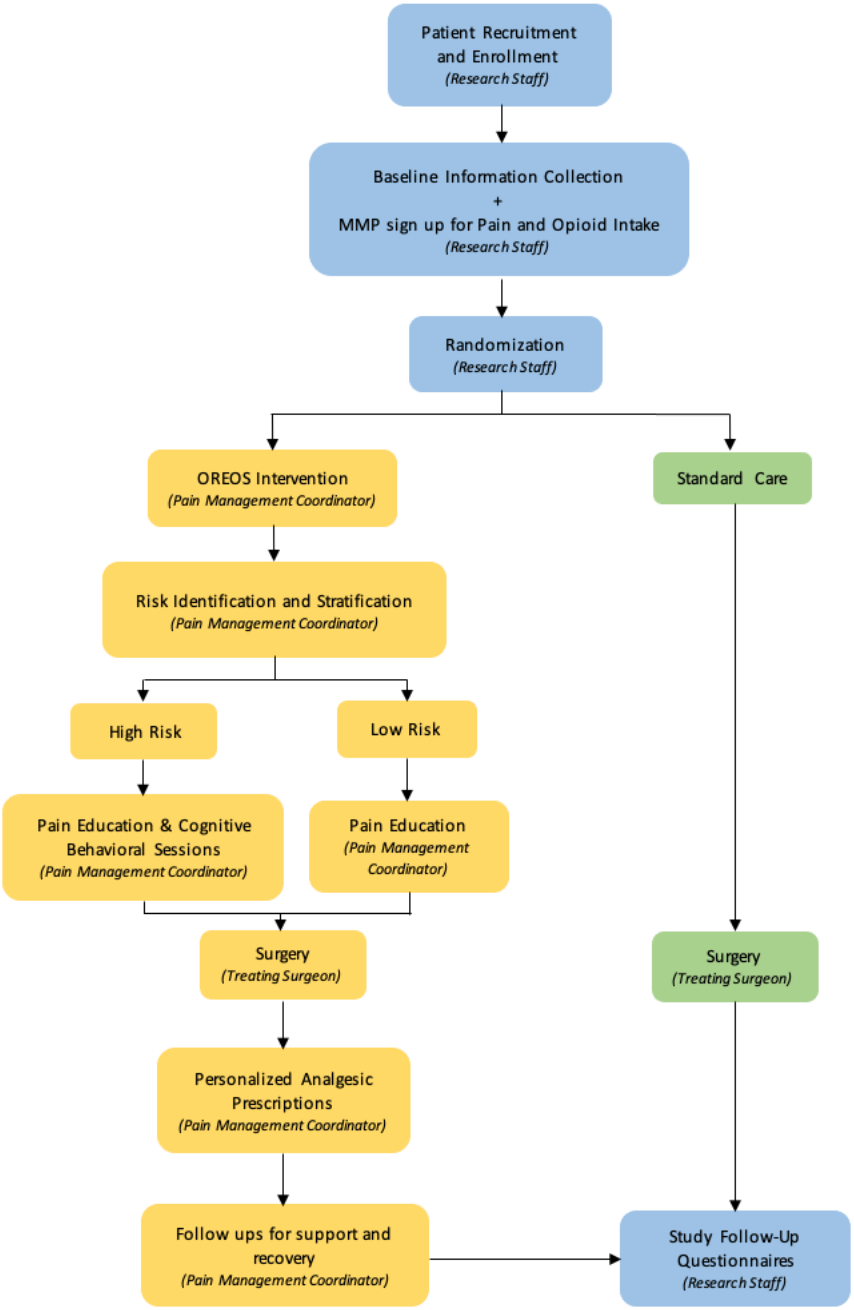

Table 1: Trial Objectives, Outcomes, and Analyses

Feasibility Objectives	***Feasibility Outcomes***	***Evaluation metrics***	***Analysis***
Intervention adherence	Percentage of patients receiving at least 3 of the 4 trial intervention components.	>90% feasible; 80-90% to consider design modifications; <80% not feasible.	Descriptive
Patient recruitment	Time to recruit target sample size	We aim to recruit 100 patients in 4 months.	
Patient retention	Percentage of follow up at 12 months	>90% feasible; 80-90%-consider design modifications; <80%-not feasible	

Clinical Objectives	***Clinical Outcomes***	***Analysis***
Opioid-free pain control	Time to three or more consecutive days of <4/10 pain score on a 0-10 NRS with no opioid use for the operated knee	hazard ratios, 95% CI; Kaplan-Meier survival curve
Presence of chronic postsurgical pain (CPSP) at 3, 6, 9 and 12 months	Presence of CPSP as adopted in the International Classification of Diseases (ICD)-11 version by World Health Organization	descriptively as point estimates and 95% CI by group, with minimally important differences presented for context
CPSP pain intensity at rest and movement	Average pain score over the previous week in 0-10 NRS	
Presence of persistent opioid use (POU)	Presence of daily opioid use, started after surgery or increased after surgery (binary)	
Satisfaction with pain control at 3, 6, 9 and 12 months	Using a 0 to 100 scale (0=extremely dissatisfied, 100=extremely satisfied)	
Return to Function at 3, 6, 9, and 12 months	Using the Return to Function questionnaire	
Knee function at 3, 6, 9, and 12 months	Using Oxford Knee Scale (OKS)	

Quality of Life	Using Euro-Qol 5 Dimensions (EQ-5D) instrument	
Economic analysis	Intervention costs and healthcare resource utilization information as well as information on productivity (e.g. time missed from work) will be collected using a self-administered questionnaire, developed for the purpose of this study.	QALYs associated with each study arm will be reported as point estimates along with confidence intervals but not compared in a formal economic evaluation.
Complications	Surgery-related and knee-related adverse events, pain medication related adverse events, readmissions, and serious adverse events (SAEs).	descriptively by group

Table 2: Schedule of Events

Study Event	Pre-op 1-6 weeks	In hospital	Postoperative weeks						Months			
			1	2	3	4	6	8	3	6	9	12
Screen and consent	X											
Identify high risk patients	I											
Pain education	I											
CBS intervention	I											
Electronic pain and opioid diary	X	X	X	X	X	X	X	X				
Check in with coordinator	I	I	I	I	I	I	I	I				
CPSP assessment[39], and pain intensity with rest and movement									X	X	X	X
Opioid use	X	X						X	X	X	X	X
Satisfaction with pain control									X	X	X	X
Return to function									X	X	X	X
Knee function	X								X	X	X	X
EQ-5D	X								X	X	X	X
Health economics									X	X	X	X
Complications	X	X	X	X	X	X	X	X	X	X	X	X

(X = All groups; I = Intervention group only)

CHAPTER 4: CONCLUSIONS

OVERVIEW

This thesis covers pain and opioid use outcome reporting in total knee arthroplasty (TKA) randomized controlled trials (RCT). As part of this thesis, I cover the introduction that outlines the problems of chronic post-surgical pain (CPSP) and persistent opioid use (POU) as important health issues in Chapter 1. This chapter is followed by a systematic review of pain and opioid use outcome reporting in arthroplasty trials in Chapter 2, and a protocol for a pilot randomized controlled trial that serves as an example for how to measure pain and opioid use as explicitly interrelated outcomes in Chapter 3. In this concluding chapter, I am summarizing my observations within each chapter.

CHAPTER 1: AN INTRODUCTION TO PAIN AND OPIOID USE IN KNEE REPLACEMENT SURGERY

The definitive treatment option for end-stage knee osteoarthritis (OA) is total knee arthroplasty (TKA). While TKA is effective, some patients still experience lasting pain and limited function postoperatively, with 8-34% of patients developing CPSP. The current approach to managing post-discharge pain following TKA is to prescribe a set of medications including opioids to every patient, but a one-size-fits-all approach does not consider individual pain trajectories or preferences. Additionally, exposure to opioids may contribute to persistent opioid use (POU), which can be associated with negative effects on the patient and society. However, existing interventions have not been successful in addressing these issues. Considering that there are several patient, system and service factors influencing the problems of CPSP and POU, multicomponent interventional

paradigms or care pathways, such as transitional pain service (TPS) have been suggested. Despite their conceptual appeal, there is lack of evidence to support the implementation of these multicomponent interventions.

CHAPTER 2: PAIN AND OPIOID USE OUTCOME REPORTING IN KNEE ARTHROPLASTY TRIALS: A SYSTEMATIC REVIEW

Key findings: Since pain severity (burden) and opioid use can influence each other, they can be considered as interrelated outcomes. To assess the number of studies and their approach to consider them as interrelated outcomes, we conducted a systematic review of the literature of published randomized controlled trials (RCTs) on knee arthroplasty. We found that only 2.1% of TKA RCTs in the past 10 years reported pain and opioid use as either multicomponent or co-primary endpoints, whereas most trials assessed these outcomes as individual entities. 44.7% of trials reported pain as a primary outcome, whereas 32.3% of trials reported opioid use as a primary outcome.

Limitations: Some limitations of this systematic review are that only studies published in English were included, "unclear" judgements for risk of bias were not clarified with study authors. Additionally, majority of the included studies were of low-quality evidence in the context of selective reporting and blinding. Lastly, we only primarily focused on TKA which limited the generalizability of the results.

Future Directions: The lack of reporting pain and opioid use outcomes as combined outcomes among TKA RCTs that assess pain management treatments is of concern, as these outcomes are often indicators of successful pain management. To address the lack of

reporting of combined outcomes, we suggest that future studies report these outcomes as either multicomponent or co-primary outcomes to consider the impact of one outcome on another (increase in opioid use decreases pain scores, and vice versa). When the conceptual interrelationship between these two outcomes is not considered, it can lead to an inaccurate assessment of treatment effects.

CHAPTER 3: OPIOID REDUCTION AND ENHANCED RECOVERY IN ORTHOPAEDIC SURGERY (OREOS): A PROTOCOL FOR A FEASIBILITY RANDOMIZED CONTROLLED TRIAL

The protocol for the OREOS pilot trial outlines the need for a multicomponent pain management pathway for minimizing pain and opioid use in patients undergoing total knee arthroplasty. We present this as an example of an RCT that uses a multicomponent endpoint to determine the feasibility of implementing and studying a pain management pathway to improve pain and opioid use outcomes. The primary objectives are to assess patient retention, adherence, and recruitment while the secondary objectives include opioid-free pain control, knee function, quality of life, and an economic analysis. As an example of a combined pain and opioid use outcome, we consider opioid free pain control and define it as pain scores less than <4/10 and no opioid consumption for three consecutive days.

The OREOS trial aims to determine the efficacy of a multicomponent pain management pathway which consists of preoperative pain and opioid use education, risk identification and mitigation, personalized postoperative prescriptions, and continued support and recovery for 8 weeks after TKA. The intervention will be facilitated by a pain

management coordinator who will liaise with the patients and circle of care to personalize care and provide support pre- and post-operatively. We believe that the results of this trial will improve pain control and reduce harms while focusing on a coordinated, patient-centered, and shared-decision making approach to care.

FINAL CONCLUSIONS

This thesis outlines pain and opioid use reporting as either multicomponent or co-primary endpoints in TKA RCTs. We look at literature to identify trials considering pain and opioid use as interrelated outcomes after surgery and suggest that future trials should consider approaches to combine them when appropriate. Lastly, we also provide a trial protocol that highlights the rationale and approach to integrate measurement of pain and opioid use at the patient level as a multicomponent endpoint. This thesis highlights the important and necessary study aspects that are needed for future research, such as evaluating pain and opioid use as interrelated endpoints to avoid wrongly concluding treatment effects of each outcome. While we focused on pain and opioid use outcomes as interrelated endpoints in TKA, the results of this thesis can be applied to other specialities that also assess interrelated endpoints.