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Complete List of Authors:	Bicket, Mark C.; University of Michigan, Anesthesiology and Health Management and Policy Ladha, Karim; University of Toronto Haroutounian, Simon; Washington University School of Medicine in St. Louis, Anesthesiology McFarlin, Kellie; Henry Ford Health System, Surgery Neff, Mary; University of Michigan McDuffie, Rachel; Washtenaw County Waljee, Jennifer F; University of Michigan Wijeysundera, Duminda; St Michael's Hospital, Anaesthesia Brummet, Chad; University of Michigan Michigan Medicine, Anesthesiology Li, Yi; University of Michigan School of Public Health, Biostatistics Investigators, CARES; N/A
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Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES): protocol for a pragmatic, international multicentre randomized trial

Protocol

Mark C Bicket, Karim Shiraz Ladha, Simon Haroutounian, Kellie McFarlin, Mary Neff, Rachel L McDuffie, Jennifer F Waljee, Duminda Nalaka Wijesundera, Chad Brummett, Yi Li, and the CARES Investigators

Correspondence to Dr. Mark C Bicket; mbicket@umich.edu

Abstract

Introduction Acute pain is commonly experienced by millions of patients who undergo outpatient surgical procedures. Moreover, an increasing number of procedures are performed on an outpatient basis, requiring greater postoperative planning to ensure effective pain management. Analgesic approaches commonly involve prescription opioids and non-steroidal anti-inflammatory drugs (NSAIDs), but an optimal regimen that balances pain and adverse effects has not been identified. In addition, critical gaps in evidence exist regarding how opioids and NSAIDs compare as analgesic regimens after surgery.

Methods and analysis The CARES Trial (Comparing Analgesic Regimen Effectiveness and Safety after Surgery) is a pragmatic, international, multicenter randomized trial that enrolls adults undergoing three elective surgical procedures (laparoscopic cholecystectomy, breast lumpectomy, hernia repair). Participants are randomized to receive discharge analgesic prescriptions that consist of either non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose opioids (i.e., 10 pills of oxycodone 5 mg or equivalent), with both groups prescribed acetaminophen around-the-clock. The primary effectiveness outcome is patient-reported worst daily pain intensity over the first seven days after surgery. The primary safety outcome is the occurrence of opioid and/or NSAID side effects over the first seven days after surgery. Secondary outcomes are assessed by patient-report and medical record review at 1 week, 1 month, 3 months, and 6 months after surgery and include sleep disturbance, patient perception of improvement/change after treatment, pain interference, anxiety, depression, health related quality of life, clinically important adverse events, substance use, opioid misuse, chronic pain, healthcare utilization related to pain, and quality of recovery.

Ethics and dissemination Investigational review boards at the University of Michigan and other sites have approved the CARES Trial. The first patient enrolled in CARES in February 2023, with recruitment anticipated through 2026. Dissemination builds on the input of patient partners and other members of an engaged stakeholder advisory board, with activities spanning co-production of summaries to share results with study participants, publications in biomedical journals and lay press, presentations to scientific and community organizations, and other multimedia communication materials.

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Strengths and limitations of this study

- The CARES trial (Comparing Analgesic Regimen Effectiveness and Safety after Surgery) examines patient-centered outcomes for two prescription analgesic regimens to treat pain after discharge from common outpatient, elective surgical procedures.
- Key outcomes include patient report of worst pain intensity and medication side effects on a daily basis in the first week after surgery, as well as recovery, health related quality of life, mental health, substance use, and opioid misuse measures up to 6 months after surgery.
- Engagement with Patient Partners and partners from community, professional, and other groups from inception to design, conduct, and eventual dissemination has increased the relevance and impact of results from CARES
- Key outcomes, which include pain and opioid use, rely on patient report and medical record review for ascertainment, and while standardized questionnaires and abstraction approaches are used, events not reported by patients or recorded in health records may be missed.
- The pragmatic design of the study permits participants to address breakthrough pain while recovering at home after surgery by receiving prescriptions for analgesics, which may lead to crossover but mimics real world care.

Introduction

Acute pain after surgery is one of the most common issues confronting patients and surgical care teams. Analgesic regimens to treat pain after discharge from outpatient surgery have commonly relied on opioid medications, with recent emphasis on non-opioid medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. While concerns about opioid prescribing for acute postoperative pain have grown, comparative effectiveness research of different analgesic regimens has not kept pace with modern day practice. Gaps in evidence exist for what constitutes the best analgesic regimen to prescribe patients after discharge from low-risk surgery.

Despite how commonly opioid and NSAID analgesic regimens are prescribed to relieve pain after low-risk surgery, little is known about how these regimens compare regarding the ability to reduce pain in the days that follow surgery. No evidence exists from randomized controlled trials regarding pain relief after surgery for time periods of 1 day or more after low-risk surgery. Additionally, no evidence exists for surgical patients who take these analgesic regimens about short-term side effects, which include nausea and constipation. Concerns also exist regarding the profile of potential side effects and harms that differ for both types of analgesic regimens, such as prescription opioid use with sedation and misuse and NSAIDs with increased bleeding risk. Data suggest that the choice of analgesic regimen may influence quality of recovery, function, and sleep after surgery, but the extent of these effects has not been well characterized for surgical patients.

The Comparing Analgesic Regimen Effectiveness and Safety for surgery (CARES) Trial evaluates multiple patient-centered pain and safety outcomes over 6 months after three of the most common outpatient surgical procedures: laparoscopic cholecystectomy, inguinal hernia repair, and breast lumpectomy. We hypothesize that patients who receive NSAID analgesic regimens will have less acute pain over 7 days after surgery when compared to patients who receive opioid analgesic regimens. Further, we hypothesize that patients who receive NSAID vs. opioid analgesic regimens will have fewer adverse medication-related symptoms and clinically important adverse events, as well as fewer disturbances in sleep over 30 days after surgery. Finally, we hypothesize that patients who receive NSAID vs. opioid analgesic regimens will have better overall quality of recovery, higher pain-related function, and greater health-related quality of life after surgery and will have less chronic pain and experience lower rates of opioid and substance misuse up to 180 days after surgery.

Methods and analysis

Study Design Overview

CARES is a pragmatic parallel arm randomized controlled trial designed to compare the effectiveness of two analgesic prescribing strategies to treat acute pain after discharge from outpatient surgery at 1 week and up to 6 months after surgery. This study compares two flexible prescribing regimens that can each be tailored to individual patient preferences. Patients are assigned to one of two arms, either 1) the NSAID arm, which emphasizes one type of NSAID non-opioid medication taken with acetaminophen, or 2) the opioid arm, which emphasizes the use of one opioid analgesic taken with acetaminophen. CARES randomizes adults undergoing one of three common low-risk surgical procedures, laparoscopic cholecystectomy, inguinal hernia repair, and breast lumpectomy, to either the NSAID or opioid arm using a 1:1 allocation. The intervention structure and data collection protocol is the same for both arms; only the prescribing strategy assignment differs between them. The CARES study group is described in online supplementary materials (Supplemental Appendix) Multiple tradeoffs between pragmatic/effectiveness and explanatory/efficacy trial designs were considered, with a full PRECIS-2 assessment to characterize these choices across 9 domains (Figure 1, Supplemental Exhibit 1).

Recruitment

For inclusion criteria, adults are eligible for participation if they have no significant analgesic medication use before surgery and undergo one of three common outpatient surgical procedures using the following definitions:
(a) No significant analgesic medications before surgery: We define significant use as over-the-counter NSAID use on >7 of 30 past days or prescriptions for analgesic medications before surgery as taking opioid or NSAID medications that are prescribed to the patient in the past 30 days, or prescription before surgery of opioid or NSAID medications by someone other than a member of the surgical team for the purposes of treating pain after discharge from surgery.
(b) One of three common outpatient surgical procedures: The three common low-risk surgical procedures include laparoscopic cholecystectomy, inguinal hernia repair, and breast lumpectomy. These procedures were selected because they are frequently performed (>5000 cases daily in the US) and involve diverse populations.[1]

As a pragmatic trial, this study enrolls a generalizable sample of surgical care patients who would be considered eligible for either NSAID or opioid analgesic therapy. We have therefore kept exclusion criteria to the minimum necessary to ensure both patient safety and internal validity. Adults who meet any of the following exclusion criteria that may interfere with providing informed consent or outcome assessment are ineligible: a) schizophrenia, bipolar disorder, or other psychosis; b) anticipated other surgery within 6 months; and c) anticipated life expectancy of less than 6 months. We also exclude patients with absolute contraindications to either prescribing strategy.

Finally, because participants should be considered eligible in clinical practice for either NSAID or opioid analgesic regimen, patients with contraindications to acetaminophen, study related NSAID drugs, and study related opioid drugs are excluded. In general, contraindications for specific medications include known allergy, liver disease or failure, estimated GFR <60 mL/min, heart failure, peptic ulcer disease, anticoagulation, heart surgery, acute psychiatric instability (defined as current uncontrolled severe depression, severe PTSD, or suicidal ideation), substance use disorder not in remission or treatment, and diversion of controlled substances.

Identifying potential participants

Potentially eligible patients of participating surgeons are identified through local searches of preoperative visits in surgical clinical schedules, anesthesia clinics, and/or local electronic health record searches for eligible patients. Searches are updated at least every month during the enrollment period.

Potentially eligible adults are contacted via phone, patient portal, or in clinic with a recruitment message describing the study. Potential participants may be contacted again within a week after receipt of this message to determine interest in participating and to assess eligibility. If the patient is eligible and interested in participating, a study staff member guides the patient through the screening and informed consent process.

Potential participants are directed to complete a screening survey to determine eligibility for the study (e.g., assess criteria like analgesic use before surgery). Potential participants may opt to either download the MyDataHelps study app for consent and screening, or complete a parallel web version. Research staff provide technical support in downloading the app used for self-administered tools and patient-reported outcomes, and check for completion of surveys. Mobile devices are provided to participants who do not have one, and use a web interface to assess any participants waiting for their device to arrive. After participants provide signed informed consent and authorization, the baseline survey is conducted via the mobile app. A second method of enrollment is in-clinic contact of potential subjects by cross-referencing the potentially eligible list with the clinic and/or surgical schedule for each participating surgeon.

This study is performed at sites where we expect approximately 50-60% of the potentially eligible population for all three procedures to be women. Eligible women and those in under-represented racial and ethnic groups are encouraged to enroll.

Randomization, Masking and Allocation Concealment

Participants provide informed consent and complete the baseline assessment before surgery. On the day of surgery, patients are randomized to the NSAID or the opioid arm. Randomization is stratified by type of surgery (laparoscopic cholecystectomy, inguinal hernia repair, breast lumpectomy) to assure balanced numbers of participants undergoing each procedure. Randomization occurs in randomly varying block sizes of 2 and 4.

Participants are not masked to treatment arm assignment due to the complexity of the masking process and patient desire to know prescribing strategies. The supervising clinical investigators who implement the interventions also are aware of treatment assignment. To maintain allocation concealment, randomization is conducted centrally using the electronic data capture form that captures the study arm assignment, using an algorithm prepared by the study statistician. Outcome assessors, who are research team members that may facilitate completion of surveys for participants in certain circumstances, are masked to treatment assignment. The masking of outcome assessors and the structured nature of outcome measures are expected to minimize potential biased ascertainment.

Interventions

The analgesic prescribing strategies in this proposal were developed from evidence-based recommendations from analgesic prescribing guidelines and systematic reviews. Each medication has demonstrated efficacy from randomized controlled trials.[2] Both prescribing strategies are operationalized by the surgical team, who provide the intervention in the form of analgesic medications prescribed to the patient, for both arms, on the day of surgery. Importantly, both the NSAID and opioid analgesic prescribing strategies are titrated to clinical response rather than a specific type, duration, or dose of treatment. This pragmatic treat-to-target approach more closely mirrors real-world practice, which tailors evidence-based treatments to patient-specific outcomes.

The NSAID analgesic prescribing strategy includes prescriptions by the surgical team for one non-steroidal anti-inflammatory drug and acetaminophen. For the NSAID prescription, the surgical team may choose among one of the following three options:

- *Ibuprofen 600 mg by mouth every six hours around the clock for three days, then as needed for pain thereafter (total #10 doses)*
- *Celecoxib 400 mg by mouth once then 200 mg every twelve hours around the clock for three days, then as needed for pain thereafter (total #10 doses)*
- *Naproxen 500 mg by mouth once then 250 mg every eight hours around the clock for three days, then as needed for pain thereafter (total #10 doses)*

The opioid analgesic prescribing strategy includes prescriptions by the surgical team for one opioid medication and acetaminophen. For the opioid prescription, the surgical team may choose to prescribe among one of the following three options, which are similar in opioid potency by morphine milligram equivalents:

- *Oxycodone 5 mg by mouth every four to six hours as needed for pain (total #10 doses)*
- *Morphine 7.5 mg by mouth every four to six hours as needed for pain (total #10 doses)*
- *Hydromorphone 2 mg by mouth every four to six hours as needed for pain (total #10 doses)*

For participants in both arms, the surgical team prescribes acetaminophen 1000 mg by mouth every 6 hours around the clock for the first three days after surgery then as needed thereafter (total #20 doses).

Medication safety considerations

Participants are informed of potential interactions and safety considerations, in line with standard of care, at the time of analgesic regimen prescribing. At study assessments, use of study medications and over-the-counter medications is evaluated. Participants receive closer monitoring than is available in usual practice. The study permits other aspects of perioperative and surgical care per the usual practices of surgical teams and does not specifically direct the use of local anesthetics provided by the surgical team in the operating room

Recommendations for prevention of constipation are provided to participants in both study arms at the outset as per the usual practice at each study site. Important adverse events (e.g., bleeding) are evaluated by a study physician and reported to the patient's surgical provider. Potentially urgent adverse events (e.g., chest pain) are referred for immediate evaluation in the local clinic or emergency department.

Data Collection

Study measures include both patient-reported measures that are collected in assessments at baseline and as outcomes in the time period after surgery. Assessments require approximately 25 minutes at baseline, 3 months, and 6 months; and approximately 15 minutes at 1 week and 1 month. A small, graded incentive (in increments increasing from USD$10 to USD$15, totaling USD$80 for completion of all surveys in the study period) is provided for each outcome assessment. Incentives of this magnitude offset costs of participation and are in the standard range used in our previous studies. No incentives are provided for daily monitoring of pain and analgesic use, which is conducted for clinical intervention purposes.

Patient-reported outcome measures and timing of administration are displayed in Table 1. Although participants are asked to complete a substantial battery of patient-reported measures in this proposed study, we perceive this outcome assessment protocol to be both appropriately comprehensive and reasonable in terms of respondent burden, and patient partners supported this approach to assessment. Outcome assessment protocols of similar length have been well tolerated in multiple previous symptom management trials involving patients with pain after surgery. Participants in these trials have also reported that they appreciated the sustained attention to their symptoms and perceived benefit from therapeutic disclosure.

Table 1: Patient-reported Outcome Assessment Schedule

Domain	Measure	Schedule					
		BL	D 1-7	1 wk	1 mo	3 mo	6 mo
Pain	Brief Pain Inventory short form surgical site worst pain	X	X	X	X		X
	PROMIS Pain interference	X				X	
	Global Rating of Change			X	X		
	Analgesic use		X	X	X	X	X
	Acute pain body map	X	X	X	X	X	
	Brief Pain Inventory short form whole body worst pain	X			X	X	X
	Chronic pain body map and symptom severity index	X				X	X

	Other postoperative pain treatments		X	X			
Adverse Effects	Symptom checklist	X	X	X	X		
	PROMIS Sleep Disturbance	X			X		
Recovery	Quality of recovery		D3	X			
Health-related quality of life	PROMIS Fatigue	X		X	X	X	
	PROMIS Cognitive Function	X		X	X	X	
	PROMIS Social Roles	X		X	X	X	
	PROMIS Physical Function	X		X	X	X	
Mental Health	PROMIS Depression	X					
	PROMIS Anxiety	X					
	Pain Catastrophizing Scale	X					
Substance use	TAPS	X				X	X
	Opioid misuse	X				X	X
	New prolonged opioid use						X
Other	Healthcare utilization				X		X

Notes: Baseline (BL), D (Day), Patient Reported Outcomes Measurement Information System (PROMIS), Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool.

Description of patient-reported outcomes

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines recommend assessment of multiple core outcome domains in pain clinical trials, including pain intensity, function, patient ratings of improvement, and symptoms and adverse events.[3] Each of these pain outcome domains is assessed with validated patient-reported measures.

1. The Primary effectiveness outcome for Aim 1 is acute postoperative pain over 7 days at the site of surgery. The Brief Pain Inventory (BPI) pain intensity score is used as the primary measure of pain intensity for acute pain over the first 7 days. BPI is also used to measure chronic pain at 180 days. Specifically, the BPI worst pain intensity, which is a 0-10 item, assesses worst pain intensity in the past 24 hours. The BPI was originally developed for use in cancer-related pain, but has been validated for use in numerous other populations, including acute pain after surgery.[4] As the primary effectiveness outcome, this is assessed over the first week after surgery. The BPI worst pain score is also used to measure whole body pain.

2. The primary safety outcome for Aim 2 is adverse medication-related symptoms. An adverse effects Symptom Checklist proactively screens patients for their report of adverse events from analgesic medications over the first 7 days after randomization, in line with pain clinical trial guidelines (**Table 2**).[5] The validated Symptom Checklist assesses the number and severity of common symptoms.[6] The list was adapted to include the most common side effects from NSAID and opioid oral analgesics for postoperative pain identified in a Cochrane review.[7] The instrument can be completed in <3 minutes. The primary safety outcome is the presence of any adverse medication-related symptoms over the first 7 days of surgery because the vast majority of patients complete analgesic use after for the procedures included in CARES by this time.

Table 2. Postoperative adverse medication-related symptoms for the CARES Trial.

Have you experienced any of these symptoms today? Select all that apply.

☐ Nausea	☐ Vomiting
☐ Constipation	☐ Diarrhea

☐ Itching (pruritus)	☐ None

Have you experienced any of these symptoms today? Select all that apply.

☐ Stomach pain	☐ Difficulty sleeping (insomnia)
☐ Heartburn	☐ Generalized weakness (asthenia)
☐ Gas	☐ Tiredness
☐ Headache	☐ Drowsiness or sleepiness (somnolence)
☐ Lightheadedness	☐ Sweating
☐ Dizziness	☐ Flushing
☐ Runny nose	☐ Rash
☐ Dry mouth	☐ Fatigue
☐ Confusion	☐ Difficulty passing urine
☐ Difficulty concentrating	☐ None

Any other symptoms you want to report _____

Symptoms can be classified as:
Mild = you notice symptoms, but they aren't a problem
Moderate = symptoms that limit of your normal daily activities
Severe = symptoms make normal daily activities difficult or impossible

For each symptom checked, user then select from the following options:
☐ Mild ☐ Moderate ☐ Severe

Notes: Adapted from the Medication Symptom checklist and Moore et al.[6,7]

3. Secondary outcomes include measures for other pertinent domains. PROMIS Pain Interference scale (SF-6a) is a validated and reliable instrument that can be completed in <2 minutes to measure pain-related function.[8–11] A 7-grade patient-reported global impression of change rating assesses patients' views of overall improvement or worsening pain.[12] Analgesic use includes assessment for the analgesic prescriptions written by the surgical team via chart review and patient-reported medication use (pills consumed [NSAID, opioid, acetaminophen], any other pain treatments). This permits an examination of adherence to the study regimen and potential crossover to the other study arm. A checklist of other postoperative pain treatments adapted from the Michigan Surgical Quality Collaborative will assess for non-prescribed treatments for pain after surgery such as ice, heat, and cannabis (**Table 3**).[13,14]

Table 3. CARES measure on other postoperative pain treatments

For Baseline: Do you currently use any of the following ways to reduce your pain? Select all that apply. If you have no pain, select "none"
For Postoperative Days 0-7: Have you used any of the following ways to reduce your pain at the site of surgery in <the past 24 hours; other time period>? Select all that apply.

☐ Ice/cold packs or cryotherapy ☐ Marijuana, cannabis, or CBD ☐ Heat packs ☐ Massage ☐ Topical drugs like Icy Hot or Salonpas ☐ Acupuncture, acupressure ☐ Exercise, yoga, or walking	☐ Watching TV/movies, reading, music ☐ Meditation, deep breathing ☐ Electrical stimulation, TENS ☐ Prayer ☐ Talking to others ☐ Other ☐ None
Other approach to reducing pain _____ (free text)	

Notes: Responses include options based on the Michigan Surgical Quality Collaborative postoperative survey, Komann, et al., and Fan et al.[13,14]

The Michigan Body Map has been validated to measure areas of chronic pain over the body. This will include questions on the symptom severity index (SSI) to enable calculation of a score representative of widespread body pain.[15,16] The Michigan Body Map will also be adapted to measure locations of acute pain over the body that may be outside the site of surgery. PROMIS Sleep Disturbance v1.0 has been validated as 4 items measuring sleep problems.[17,18] Quality of recovery is assessed via the internationally validated Quality of Recovery-15 score, which details five domains about how well a person recovers after surgery.[19,20] PROMIS Preference score (PROMIS 29+2 Profile v2.1) is a health-related quality of life measure that has demonstrated validity.[21] It provides PROMIS scores for Cognition (Cognitive Function and Cognitive Function Abilities), Depression, Fatigue, Physical Function, Ability to Participate in Social Roles/Activities, as well as Pain Interference (4a) and Sleep Disturbance. PROMIS Anxiety includes 4 questions about anxiety. The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool consists of a 4-item screening for tobacco use, alcohol use, prescription medication misuse, and illicit substance use in the past year and brief assessment.[22,23] One question from the National Survey on Drug Use and Health (NSDUH), a national survey with established validity and reliability, assesses for opioid misuse defined as use that is more than prescribed, for non-pain-related reasons, or in a way not prescribed by a doctor.[24,25] New prolonged opioid use, defined as filling ≥1 opioid prescription post-discharge between 4 and 90 days and also between 91 and 180 days, will be assessed by patient report.[26] Patients will also be asked to report on healthcare utilization at 1 and 6 months after surgery, including unplanned postoperative clinical interactions related to pain (patient messages, phone calls, non-routine clinic visits related to pain), emergency room visits, and hospitalizations.

Description of other measures

At baseline, patients complete questions on demographics,[27–33] a comorbidity checklist derived from the Charlson index,[34] treatment expectations (**Table 4**), depression (PHQ-2),[35] anxiety (GAD-2),[36] the pain catastrophizing scale (PCS short from 6),[37] and preference on the return of study results. The local study team reviews a patient's chart to examine for characteristics of the perioperative period, procedure, and PACU course. The local study team reviews a participant's chart to assess for clinically important adverse events at the end of the study period. This review also assesses for unplanned postoperative clinical interactions related to pain including patient messages, phone calls, non-routine clinic visits related to pain. This also assesses for emergency room visits, hospitalizations, and 30-day

complications after discharge measured using the American College of Surgeons' (ACS) National Surgical Quality Improvement Program (NSQIP) definitions.[38]

The central study team assesses new prolonged opioid use by obtaining prescription drug monitoring program data, if available. Data necessary for linkage includes name (first, last), date of birth (month/day/year), and gender.

Table 4. CARES measure on expectations prior to surgery

Statement or Question	Responses
Please indicate your expectations regarding your surgery and health care team, using a 0 to 10 scale, for the following items. *(Randomize list)*	-
1. How much functional ability do you expect to have after you recover from surgery?	0=expect no ability (maximum impairment), 10=expect to be fully functional
2. I expect that the pain related with this surgery will relieve over time.	0=expect no pain relief, 10=expect full pain relief
3. I'm afraid of pain or other complications during and/or after surgery.	0= not at all afraid, 10=extremely afraid
4. Please rate how much pain you expect to have by circling the one number that best describes your expected pain on the first day after you recover from surgery.	0=expect no pain, 10=expect pain as bad as you can imagine
5. Please rate how much pain you expect to have by circling the one number that best describes your expected pain at one month after you recover from surgery.	0=expect no pain, 10=expect pain as bad as you can imagine
6. I expect that the pain related with this surgery will be relieved by taking prescription strength non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib, or naproxen.	0=expect no pain relief, 10=expect full pain relief
7. I expect that the pain related with this surgery will be relieved by taking prescription strength opioid drugs such as oxycodone, morphine, or hydromorphone.	0=expect no pain relief, 10=expect full pain relief
8. I expect to experience side effects from prescription strength non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib, or naproxen that I take to relieve pain after surgery.	0=expect no side effects, 10=expect side effects as bad as you can imagine
9. I expect to experience side effects from prescription strength opioid drugs such as oxycodone, morphine, or hydromorphone that I take to relieve pain after surgery.	0=expect no side effects, 10=expect side effects as bad as you can imagine
10. What treatment group do you prefer to be in?	NSAIDs, Opioids, No preference

Trial Data Sources

A mature and integrated digital informatics infrastructure is employed in CARES using CareEvolution MyDataHelps. Data gathered by patient report via the study app MyDataHelps participant portal is integrated into the trial data. Research participants consent using the app, complete patient reported outcome measures, and receive return of results. If patients do not have a mobile device, they may use a study participant portal to complete patient-reported

outcomes. As a final step to ensure complete follow up, research coordinators may contact patients to assist with completion of participant provided information if necessary. Sites use MyDataHelps to document patient screening, approach, consenting, and enrollment using electronic case report forms (eCRFs). MyDataHelps includes customizable, data-driven eCRFs to capture data gathered by research coordinators at each site. Standardized data forms capture data from the perioperative period including immediately before, during, and after surgery. MyDataHelps has been used to document clinical quality projects and prospective observational research, and has met strict medicolegal, audit trail, electronic signature, and disaster recovery requirements across federal and state regulations.

Prevention of Missing Data

In pain clinical studies, dropouts often occur due to intervention-related factors (e.g., adverse effects, lack of treatment efficacy) and missing data can pose a substantial threat to internal validity. CARES has several design features meant to enhance participant retention and reduce missing data. First, the interventions are flexible treat-to-target analgesic prescribing strategies that allow tailoring to each type of procedure for patients. Second, both study arms are active interventions, which should reduce differential dropout that can occur among patients assigned to a control arm. Third, randomized participants are strongly encouraged to complete all outcome assessments, and individuals who do not respond to the study app assessment receive in-app reminders and phone call reminders from study staff. Fourth, to reinforce participants' sense of commitment to the study, participants receive quarterly CARES newsletter including tips on pain management and positive news related to recovery from surgery. Finally, if participants are at risk of dropping out due to assessment burden, they are given the option of completing a minimum core assessment comprising primary pain (i.e., BPI) and adverse effect (e.g., symptom checklist) measures.

Sample Size and Power

The sample size for CARES was calculated based on testing the superiority of NSAID versus OPIOID analgesic regimens on effectiveness for acute pain. Because the surgical community has considered pain and post-discharge prescribing guidelines in the context of specific types of surgical procedures, the trial is powered to test the superiority for each one of the three types of low-risk surgeries included in CARES (i.e., gallbladder removal, inguinal hernia repair, breast lumpectomy).[39–43] To account for multiple comparisons, a two-sided Type I error of 0.016 after applying a Bonferroni correction was used to control the family-wise error rate of 0.05 with three procedure types. Also, 90% power testing was used for superiority (two-sample t test) at the Day 7 assessment, but achieved power in the GEE models will be improved by the repeated outcome measures. The outcome measure for BPI pain intensity has a mean of ~3.4 (standard deviation of 2.1) in prior samples of low-risk surgical patients, and past studies suggest a difference of 1.0 represents a minimally important difference.[44–46]

For the superiority analysis, calculations in Stata estimated that 244 patients (or 122 per arm with 1:1 allocation ratio) were required to detect a difference in means of >=1. Based on prior work, we conservatively assume a 15% crossover or loss to follow up. This requires enrolling 288 patients per type of surgery. To account for the three types of surgery, the study anticipates recruiting a total study population of 900 (300 patients per type of surgery).

The CARES Study is also powered to examine heterogeneity of treatment effects and detect differences for subgroup analyses. After testing for effect modification, tests for examining outcomes among a priori selected subgroups will occur based on differences in acute pain, opioid prescribing, and access to pain care.[41,43,47] These subgroups include: (1) male/female patients; (2) age <65/>=65 years; (3) black/white patients; and (4) urban/rural patients. We calculated power for the effectiveness of subgroups, using the total study population and Bonferroni adjustment for 8 prespecified comparisons (2 each for sex, age,

race/ethnicity, and urban/rural, with P values <0.00625). We anticipate the smallest subgroup size to be >=15% of the total sample.

Data and Safety Monitoring

The study team formalized the data safety monitoring plan and formed an independent data safety monitoring board (DSMB) for CARES in consultation with the funder. The CARES DSMB provides independent review of the study to ensure the safety of participants and the validity and integrity of the data. Its members include relevant context experts (e.g., surgeon, anesthesiologist, biostatistician with clinical trials experience, Patient Partner, et al.) and a DSMB Chair. The CARES DSMB charter was written and approved by concerned parties. The CARES DSMB meets two to three times per year.

Plans include for data by treatment group to be seen by the CARES DSMB after enrollment of the first 100 patients, and after 25%, 50% and 75% accrual of the sample; the CARES DSMB has sufficient data to assess data integrity and to compare rates of adverse events between treatment arms that may raise safety concerns. The CARES DSMB may consider termination at any point based on unexpected safety findings; however, early stopping criteria are not planned due to apparent benefit since neither approach is experimental, both approaches are widely used, and because substantial evidence from an adequately powered trial is needed to affect clinical practice. The initial CARES DSMB meeting focused on review and approval of the study protocol and its informed consent template. Thereafter, the CARES DSMB reviews primary and secondary safety outcome data, data quality, enrollment data and projections.

Patient and public involvement

We have engaged and will continue to engage with patient partners, who are patients or caregivers with lived experience with each of the three included types of procedures as well as being prescribed and using one or more of the study medications for pain relief. We have also engaged with other important stakeholders to develop CARES for several years using a variety of approaches. We conducted a patient-preference survey among 42 persons before surgery, which indicated that 71% would join the study and be randomized.[48] Survey results also informed the study design, in that many respondents indicated reticence in participating in the study were their analgesic regimen to be masked. In partnership with the Michigan Institute for Clinical and Health Research, we convened a Community Engagement Studio to share a synopsis of the study protocol and learn the perspectives of twelve Patients with Lived Experience. In the studio, patients offered feedback regarding the primary and secondary outcomes for the study, including identifying two outcomes of key importance (pain intensity, adverse events), as well as the recruitment strategy and factors regarding whether they would participate. Further, one of the CARES study co-investigators has experience as a caregiver and leader involved in relevant community organizations.

CARES also engages with patient and public members by convening a Stakeholder Advisory Board that includes five patients partners who include patients with lived experience and seven non-patient stakeholders. The CARES Stakeholder Advisory Board meets three to four times per year, where members offer perspectives and feedback that have informed the design and conduct of the study, and informs the dissemination of results. For example, Patient Partners and members of the Stakeholder Advisory Board reaffirmed and clarified the primary effectiveness and safety outcomes for the CARES Trial. Patient Partners identified worst pain after surgery, pain happening on the earliest postoperative days (i.e., postoperative day 1 or 2), and side effects from pain medications as among the most important and relevant outcomes based on their experiences. In collaboration with our Patient Partners and other stakeholders, priority was given to the following questions faced by surgical patients requiring prescription medications to treat pain: (1) Will the analgesic regimen that I receive adequately relieve my

acute pain as I recover from my surgery? (2) Will my analgesic regimen influence my risk of experiencing an adverse effect as I recover from my surgery? And (3) Will my analgesic regimen influence the quality of my recovery, my ability to function free of pain, my quality of life, my risk of experiencing chronic pain, and my risk of either misusing opioid medications or using other substances? Patient partners and stakeholders also helped to select additional measures based on patient-centeredness, validity, reliability, sensitivity, and brevity, with focus on reducing patient burden.

Collaboration with the Stakeholder Advisory Board including Patient Partners includes framing results from the CARES Trial in ways that are understandable and impactful to the millions of patients who undergo low-risk outpatient surgeries every year. Co-production of three types of content and content summaries for the CARES Trial is planned, which include lay language text summaries of overall study findings, contextual text summaries that include insights relevant to different study subgroups, and digital multimedia summaries that use video, audio, and other media.

Ethics and Dissemination

The CARES trial Institutional review boards at participating sites have approved the CARES trial, including at the University of Michigan. The first patient was recruited in February 2023. Enrollment is anticipated to continue until 2026. A model consent form is provided in supplemental material Exhibit 2.

CARES Trial results have significant potential for reproduction, dissemination, and implementation across the U.S and Canada. The CARES Trial proposal has been carefully designed to include characteristics that maximize the ability to replicate study findings and put findings into practice in diverse care settings. The two comparators of NSAID and opioid analgesic regimens represent readily available medications already in widespread use as prescribed by surgeons to patients after low-risk outpatient surgery. The flexibility built into the two regimens increases their ability to be used by more patients and in more care settings. By including three different types of low-risk surgery and focusing on four different types of patient subgroups, the ability to apply this work to varied types of surgery and groups of patients is enhanced.

Unique opportunities exist to disseminate findings from the CARES Trial beyond traditional academic venues. Existing infrastructure includes the Overdose Prevention Engagement Network (OPEN) to support dissemination activities.[49] Past evidence of OPEN dissemination includes reference for guidelines by federal entities including the Centers for Disease Control and Prevention and national quality organizations including the Leapfrog Group.[50] OPEN meets with various stakeholders within the state of Michigan and across the nation, and these meetings serve as an additional mechanism to disseminate this work. Through the Institute for Healthcare Policy and Innovation (IHPI) at the University of Michigan, a robust team of liaisons engage with Federal and state legislators, and dissemination will continue through one-on-one meetings and organized events coordinated by these channels. The Stakeholder Advisory board will help design digital multimedia communication materials and share information through events relevant to broader communities. Partnership with the Michigan Surgical Quality Collaborative, which engages with all major hospitals across Michigan, and Blue Cross Blue Shield of Michigan, is planned to disseminate study findings from the CARES Trial, similar to our previous work in reducing opioid prescribing while maintaining patient-reported outcomes.[51–53]

Consideration for possible barriers to disseminating and implementing the results from the CARES Trial has been given. Some patients may hesitate to accept findings favoring either NSAID or opioid regimens, due to the personal nature of pain. To address this issue, data elements include patient-reported outcomes for pain, adverse events, and important secondary outcomes after surgery. Examination of how well and how safe these regimens work in diverse

groups of patients is planned, as well as collaboration with the Stakeholder Advisory Board including Patient Partners in order to frame results from the CARES Trial in ways that are understandable and impactful to the millions of patients who undergo these low-risk outpatient surgeries every year. Surgical providers may hesitate to adopt findings from CARES for low-risk procedures and only adopt findings for certain types of procedures; for this reason, CARES includes three types of low-risk procedures that vary by important patient characteristics such as age, sex, and body region. CARES Trial findings for NSAIDs vs. opioid may differ among key patient subgroups, type of procedure, or other important features, which may disallow for one consistent message about which analgesic regimen is best. If this happens, the study will adapt messaging and tailor results for each group to align with evidence from the trial.

Conclusion

The CARES Trial is a pragmatic randomized controlled trial that enrolls adults who undergo three common outpatient surgical procedures in order to compare NSAID versus low-dose opioid analgesic regimens with respect to pain, adverse effects, and other significant patient-centered outcomes. By leveraging the expertise of an engaged stakeholder advisory board, as well as diverse recruitment settings that span academic and community health systems, the CARES trial will generate critical evidence to help determine the best post-discharge analgesic regimen that maximizes pain relief while minimizing adverse effects for millions of patients who undergo these procedures every year.

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Figure 1. CARES Trial PRECIS-2 Wheel.

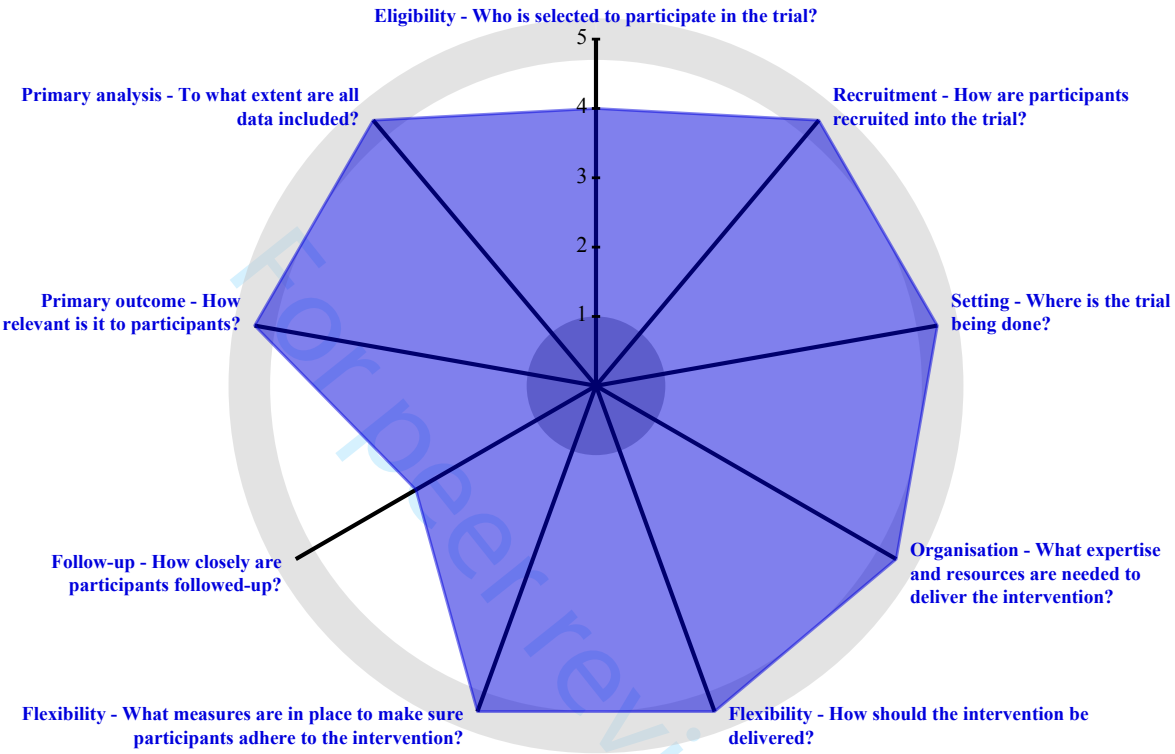
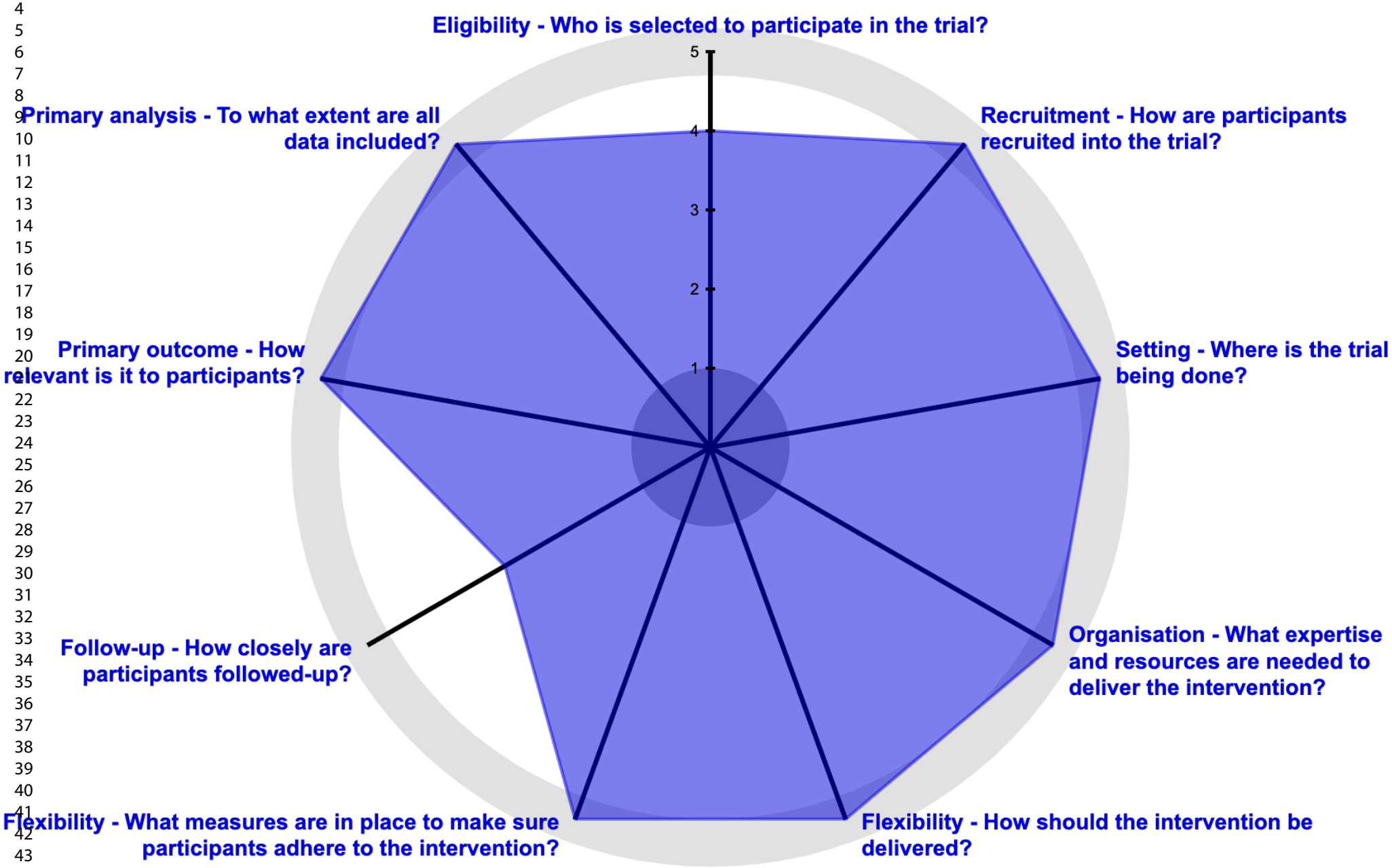


Figure 1 Legend: Nine listed domains for the Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) study and the PRECIS-2 Wheel are described in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.



Appendix: Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) Investigator Group
January 2025

CARES Research Team
Principal Investigators:
Mark Bicket, MD, PhD (Principal Investigator), University of Michigan, Ann Arbor, MI
Karim Ladha, MD, MSc, University of Toronto

Co-Investigators:
Chad Brummett, MD, University of Michigan
Simon Haroutounian, PhD, Washington University in St. Louis
Yi Li, PhD, University of Michigan
Kellie McFarlin, MD, Henry Ford Health System
Mary Neff, CRNA, University of Michigan
Jennifer Waljee, MD, MPH, MS, University of Michigan
Duminda N. Wijeysundera, MD, PhD, University of Toronto

Data Coordinating Personnel:
University of Michigan, Ann Arbor, MI
Sarah Clark, BA (Project Manager)
Kendall Dubois, MS (Project Manager)
Alicia Sudayam, BS (Engagement Coordinator)
Vidhya Gunaseelan, MBA, MS, MHA (Lead Data Analyst)
Chiao-Li Chan, MSW (Data Analyst)

CARES Sites
Henry Ford Hospital, Detroit, MI
Principal Investigator: Kellie McFarlin, MD
Site Coordinator: Daniel Molitor, Olivia Dionisio

Washington University St. Louis, St. Louis, MO
Principal Investigator: Simon Haroutounian, PhD
Site Coordinator: Justin Stout, MS

Unity Health Toronto, Toronto, ON, Canada
Principal Investigator: Karim Ladha, MD, MSc
Co-Investigator: Duminda N. Wijeysundera, MD PhD
Site Coordinators: Zaaria Thomas, BA; Roshni Nayar, BSc; Janneth Pazmino-Canizares, MSc; Tedros Mokonnen, BSc

Temple University, Philadelphia, PA
Principal Investigator: Ellen Hauck, MD
Site Coordinator: Adam Lloyd-Jones, BA

Cooper University, Cooper, NJ
Principal Investigator: Wray Hughes, MD
Co-Investigators: Ludmil Mitrev, MD; Lawrence Mulligan, MD

CARES Surgeons
University of Michigan, Ann Arbor, MI

Bess Connors, MD; Justin Dimick, MD, MPH; Lesly Dossett, MD, MPH; Jonathan F. Finks, MD; Tasha Hughes, MD, MPH; Desmond Tuan-Khai Huynh, MD; Grace J. Kim, MD; Nabeel Robert Obeid, MD; Melissa Louise Pilewski, MD; Jenny Meng Shao Kashmanian, MD; Dana Telem, MD, MPH

Henry Ford Hospital, Detroit, MI
Kellie McFarlin, MD; Anthony Falvo, DO; Sina Khoshbin, MD, Kurt Kravalovich MD, Marianne Franco MD, Matthew Madion MD, Abbas Al-Kurd MD, Srinivas Bhandakar MD, Christopher Steffes MD, Oliver Varban MD, Robert Elkus MD

Washington University St. Louis, St. Louis, MO
Rebecca Aft, MD, PhD; Michael M. Awad, MD, PhD; Jeffrey Blatnik, MD; Michael Brunt, MD; Katherine Glover-Collins, MD, PhD; Arnab Majumder, MD; Julie Margenthaler, MD; John A. Olson, Jr., MD, PhD

Unity Health Toronto, Toronto, ON, Canada
Ralph George, MD; David Gomez Jaramillo, MD, PhD; Joao Rezende-Neto, MD, PhD; Jory Simpson, MD, MEd; Brent Hopkins, MD; Morgan Schellenberg, MD; Anna Dare, MD PhD; Najma Ahmed, MD; James Jung, MD PhD

Temple University, Philadelphia, PA
Jessica H. Beard, MD, MPH; Elizabeth D. Dauer, MD; Christina Jacovides, MD; Neil A. King, MD; Zoe Maher, MD; Cristina L. Novak, MD; Abhijit Pathak, MD, MS; Matthew Philp, MD; Mary T. Pronovost, MD; Thomas Santora, MD; Rohit Soans, MD

Cooper University, Cooper, NJ
Umur Atabek, MD; Maureen Moore, MD; Robert Simons, MD

CARES Stakeholder Advisory Board
Lead Stakeholder:
Rachel L. McDuffie, MPH, JD

CARES Patient Partners:
Deidre Bauer
Louis Daher
Carl Henscie
Elizabeth Racz

CARES Stakeholders:
Kanzoni Asabigi, MD, Detroit Area Mental Health Leadership Team
James Grant, MD, Blue Cross Blue Shield of Michigan
Tasha Hughes, MD, Breast Surgeon
Clifford Ko, MD, American College of Surgeons
Gregory Terman, MD, US Association for the Study of Pain

CARES DSMB:
Christopher Wu, MD, (Chair) Hospital for Special Surgery, New York, NY
Michael Smith, PharmD, (Vice Chair) The University of Michigan, Ann Arbor, MI
Gail Einhaus (patient representative), Ann Arbor, MI
Ed Mariano, MD, MAS, Stanford University, Stanford, CA
Blair Richards, MPH, The University of Michigan, Ann Arbor, MI

Supplemental Material for

Bicket MC, Ladha K, Haroutounian S, McFarlin K, Neff M, McDuffie R, Waljee J, Wijesundera DN, Brummett CM, Li Y. Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES): protocol for a pragmatic, international multicentre randomized trial. BMJ Open. 2025

NCT05722002

Supplemental Exhibit 1. PRECIS-2 assessment for the CARES trial.

Supplemental Exhibit 2. Model consent form for CARES trial.

Supplemental Exhibit 1. PRECIS-2 assessment for the CARES trial.

Domain	Assessment
1. Participant eligibility	Since this study will enroll all patients without contraindications to opioids, NSAIDs, or acetaminophen having a surgery of interest across 4 diverse academic and community sites across the US, it is highly pragmatic in this domain.
2. Participant recruitment	Recruitment will take place in usual care settings so that people are recruited after they present to surgery clinics to have a surgery of interest and will draw from multiple clinical sites as an explicit way of increasing applicability of trial results. The study is extremely pragmatic in this domain.
3. Care setting	This study setting will include identical settings to the usual care setting for the analgesic regimen interventions, and include surgery clinics at multiple academic and community sites that treat a patient sample with socioeconomic and ethnic diversity. The study is maximally pragmatic in this domain.
4. Organization resources, expertise, and care delivery	The study includes the prescription of analgesic regimen interventions within the usual organization of care for surgical patients and requires no extra clinicians, training, or expertise to deliver the interventions. The study is maximally pragmatic in this domain.
5. Flexibility of intervention delivery	Treating surgeons and surgical providers will receive brief, simple, and flexible care protocols for patients randomized to analgesic regimens after surgery; these protocols will state explicitly that co-interventions will be permitted based on clinical judgment. The study is maximally pragmatic in this domain.
6. Flexibility of adherence for participants	Treating surgeons and surgical providers will receive brief, simple, and flexible care protocols for patients randomized to analgesic regimens after surgery; use of the analgesic regimen interventions will be measured but not enforced and patients may receive alternative treatments if needed. The study is maximally pragmatic in this domain.
7. Follow-up intensity	Follow-up will occur via a patient-reported smartphone app over 1 week, then 1-, 3-, and 6-months after surgery. Opioid use will be assessed by searches of prescription drug monitoring program data. The study is moderately pragmatic in this domain.
8. Relevance of primary outcome	The primary outcome (pain intensity after surgery at 1 week) is simple and pragmatic; secondary outcomes are also pragmatic endpoints, including side effects, quality of recovery, pain interference, and opioid use.
9. Analysis of primary outcome	All randomized patients will be included in the primary analysis. A priori subgroups will be examined, and adjusted for compliance with the study protocol will only occur in additional analyses. The proposal is highly pragmatic in this regard.

Notes: Nine listed domains for the Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) study and the PRECIS-2 Wheel are characterized in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.

Supplemental Exhibit 2. Model consent form for CARES trial.

<SITE> CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: Comparing Analgesic Regimen Effectiveness and Safety for surgery (CARES) Trial

Company or agency funding the study: Patient-Centered Outcomes Research Institute

Principal Investigator: <name>
Study Coordinator: <name>

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the research team about the study and ask them any questions you have.

You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctors. Research studies hope to learn new information about how safe and effective treatments are. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies also have different kinds of risks and risk levels, depending on the type of the study. Some studies do not offer the possibility of receiving treatment, while other studies do. You may also need to think about other requirements for being in this study. For example, some studies require you to answer questions related to your health over several weeks or months. This may require you to change your schedule, find time in your day to respond, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

Pain is a common experience after surgery. Clinicians (like your surgeon) usually choose between two strong pain relievers when prescribing medicine to take home to treat this pain.

We know that both options are effective at treating pain. These options are used every day across the United States by individuals who have the same type of surgery that you will be having. These options are:

Option 1	Option 2
A prescription for non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (Tylenol) Examples of NSAIDs: Ibuprofen, naproxen, celecoxib	A prescription for low-dose opioids and acetaminophen (Tylenol) Examples of opioids: oxycodone, morphine, hydromorphone

This study will compare these two commonly used types of medication. We know that each option works well to manage pain after surgery, but we do not know how they compare to one another. Persons who join the study will receive a prescription for one of these two options. If you join the study, you will decide whether to take the pain medication and, if you do, how much to take. If the medication is not helping to manage pain at home after surgery, you may contact your surgical team and receive any additional treatments they think are appropriate.

Just like all medications, both options may lead to side effects. NSAIDs may cause heartburn, headache, or drowsiness. Opioids may cause sedation, dizziness, nausea, or constipation. Both types of medications could also result in other side effects.

The goal of this study is to answer two key questions faced by patients who need pain medication while recovering after surgery:

- Which option is better at relieving my acute pain?
- Which option lowers my risk of experiencing a side effect?

If you join the study, on the day of your surgery you will be assigned to receive one of the two pain medications options above. You will complete a series of surveys that tell us how well the medication relieves pain, report any side effects, and share how you are recovering after surgery. The research team will also review your health and prescribing records to learn more about how well you recover. The expectation is to have a de-identified dataset at the conclusion of the study.

Randomization: This study involves a process called randomization. This means that the medication to treat your pain after surgery will not be chosen by you or the research team. If you join the study, you will be assigned by chance, like the flip of a coin, to one of the two groups. If you join the study, you need to be comfortable with the possibility of receiving either type of medication to treat your pain after surgery.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include poor pain control or discomfort with study questions. More detailed information will be provided later in this document.

This study may not offer any benefit to you now but may benefit others in the future by determining the best way to treat pain after surgery. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be six months.

You can decide not to be in this study. Alternatives to joining this study include not joining this study or joining a different study. Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Pain after surgery is common, and two types of pain relievers provide very good pain relief after surgery. One option is to take prescription nonsteroidal anti-inflammatory drugs (NSAID) with acetaminophen (Tylenol). The alternative is to take prescription low-dose opioid medications with acetaminophen. This study is being done to learn which option works the best at relieving pain and has the least amount of side effects.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Adults having one of three common surgical procedures can take part in the study if they do not have significant pain medication use before surgery. The three procedures are gallbladder removal, hernia repair, and breast lump removal.

Persons who are unable to take commonly used pain medications are not eligible. Those pain medications include Tylenol (acetaminophen), non-steroidal anti-inflammatory drugs (ibuprofen, celecoxib, naproxen), or low-dose opioid medications (oxycodone, morphine, hydromorphone). People who anticipate having more than one surgery within 6 months are also not eligible.

3.2 How many people are expected to take part in this study?

900 persons are expected to participate, <#> at <site name> and <#> at other sites around the United States and Canada.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

A — General study procedures

- We will ask you questions using surveys that can be completed on mobile devices, computers, or by telephone calls. Patients who do not have a mobile device will be provided one by the study. Provided mobile devices will have limited data that is purchased by the study team to allow for survey completion. At the end of the 6 month participation period we ask that you return the mobile device. You can either email us at <study email> or call us at <study phone> and we will send you a return envelope to return the device.
- Before surgery (up to two weeks prior), you will answer several questions in a survey that will act as a “baseline” for comparisons to questions asked later in the study.
- You will be randomized to one of two options to treat pain at home after discharge from surgery.
    - Option 1 - acetaminophen with a non-steroidal anti-inflammatory drug.
    - Option 2 - acetaminophen with a low-dose opioid.
- You will have a 50:50 chance of being assigned to each of the two options.
- Your surgical team or the research team will prescribe you one of the two options to treat pain after surgery. Receiving a prescription for medication to treat your pain after surgery is a part of your routine care.
- You will know which option you are assigned to because you will be given the prescriptions to take to the pharmacy.
- You will be asked to complete a brief survey after surgery every day for one week.
- You will be asked to complete other surveys after surgery at 1 week, 1 month, 3 months, and 6 months after surgery.
- The research team will look at your health records to understand your experience during and after surgery. These will include your surgical and medical care and prescription

medications in the electronic health record, and prescription medications in the <name of Prescription Drug Monitoring Program>.

- Results from the surveys and study measures will not be a part of your routine clinical care. Completing surveys and study measures are only part of the research study.
- After the study, you will have the option to learn about the published results from the study. These results are not individualized.

By participating in this research study, you will have certain responsibilities, like making sure that you fill out all of your scheduled surveys and reporting any adverse reactions you may have during the study. An adverse reaction is any unexpected or dangerous reaction to a medication. The adverse reaction may be sudden like anaphylaxis or develop over time like gastrointestinal bleeding. If you experience any symptoms and/or injuries during the whole duration of your participation in the study, please report these to the study team at <study email>.

B – Sub-study with specified design

<Information on substudy, if applicable to site>

C – Collection for unspecified future research

The following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

You can take part in the main study even if you decide not to let us keep your medical information for future research. If you give us your permission, we will use your medical information for future research. Even if you give us permission now to keep some of your medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your medical information, we may not be able to take the information out of our research.

We may share your medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your medical information with other researchers, we will not be able to get it back. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your medical information. Allowing us to do future research on your medical information will not benefit you directly. With appropriate permissions, your collected information may also be shared with other researchers here, around the world, and with companies. Your identifiable private information may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

4.2 How much of my time will be needed to take part in this study?

You will fill out surveys before your surgery and after you are discharged from surgery. Before surgery the surveys should take 20-30 minutes to complete. We will ask you to fill out a daily survey for the first week that is expected to take less than 5 minutes each day. After that, we will ask you to complete surveys less often - at least three times over the next 6 months. Each survey should take about 15 minutes.

4.3 When will my participation in the study be over?

Most subjects will complete their part in the study within about **6 months.** The entire study is expected to last about **3 years**.

4.4 What will happen with my information and/or biospecimens used in this study?
Your collected information may be shared with the Patient-Centered Outcomes Research Institute.

With appropriate permissions, your collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The risks to joining this study are not expected to be any greater than the risks associated with taking typical pain medications prescribed after surgery. The known or expected risks, and steps to minimize these risks, are as follows:

1. Inadequate or poor pain control after surgery:

   Background: The two options in the study are common pain-relieving medications. Both options are in routine use by patients having your surgery and are recommended by clinical guidelines. Since the two medication options being compared in the study are the most commonly used ways of treating post-surgical pain, the risk of inadequate pain control is expected to be similar to usual care.

   Steps taken by the research team to minimize this risk: The two options chosen for this study have been shown to effectively treat pain after surgery. Ensuring that your pain is treated adequately is a top priority of the study. By participating in this study, you will still be able to receive additional pain medication from your surgical team if you need it.

   If you experience poor pain control, you will be encouraged to contact your surgeon just as you would do were you not in the study. Your surgical team will learn about your pain and determine the most appropriate next step.

   After speaking with your surgical team, you may be able to take additional doses of the medication you are prescribed after surgery. If pain control continues to be a problem, your surgical team may prescribe you a different type of medication to help with your pain. You may receive additional pain treatments at their direction.

2. Discomfort from being asked personal questions on sensitive topics:

Background: This risk may result from being asked personal questions on sensitive topics. It is expected to be rare.

Steps taken by the research team to minimize this risk: Any person becoming distressed while completing questions will be encouraged to pause and ask a study team member to clarify and/or discuss the item that they find to be unclear or troubling. If needed, the person may skip any question that they find distressing.

3. Side effects from pain medication:

Background: All medications can have side effects, including those included in the study. Side effects from both types of pain medications are expected based on reports from patients who have taken these medications in the past.

Steps taken by the research team to minimize this risk: Doses for both types of pain medications are within the range that are usually given after surgery. You will be asked about any side effects in study surveys. You may stop taking the pain medications at any time that you choose. You may also contact the surgical team to discuss any significant side effects as you would if you were not in the study.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy, including a certificate that adds special protections for confidentiality to your data.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The research team has taken steps to minimize the risks of this study. Even so, you may still have problems or side effects as a part of this study, even when the study team is careful to avoid them. Telling the research team about side effects is a planned part of this study.

Please tell the researchers listed in Section 10 about any injuries or other problems that you have during this study. You should also tell your regular doctors. If you have a complication or adverse effects, the research team will communicate with your surgical team to determine the best next step. A medication dose could be lowered, stopped, or changed to a different medication.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the research team involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. However, others may benefit from the knowledge gained from this study. Findings from this study have the potential to help people undergoing surgery, their families, and their doctors make choices about how to manage pain and take the best type of pain medicine.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the research team will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined

the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?
Your surgeon would typically prescribe one of the two medication options for acute pain after surgery without participating in the study. There may be other ways of treating your pain after surgery, including using only Tylenol or using non-medication treatments.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the research team why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10.

7.2 Could there be any harm to me if I decide to leave the study before it is finished? No. Harm is not anticipated if you decide to leave the study before it is finished.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the research team may need to end your participation in the study. Some examples are:

- The research team believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the research team.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Prescription medication to treat your pain after surgery
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer. By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You are eligible to receive up to $80 for completing participation in the study. You will receive the $80 via a reloadable gift card that is sent out. You can expect the funds within 1-2 weeks of

completing the surveys for each timepoint. This includes completing the baseline survey ($15) and surveys after surgery including daily short surveys in the first week ($15 total), the 1 week survey ($10), 1 month survey ($15), 3 month survey ($10) and 6 month survey ($15). If you decide to leave the study early, you will not be paid for the surveys that you did not complete.

8.3 Who could profit or financially benefit from the study results?
No person or organization has a financial interest in the outcome of the study. Research can lead to new discoveries, such as new tests, drugs, or devices. The research team, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my information?
Research records will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the research team to link the information to you. The file is an electronic file that is stored via the cloud/shared drives. Only approved members of the research team will have access to the files.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The research team with this Certificate may not disclose or use information or documents that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use.

Information or documents protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency funding the project that is needed for auditing or program evaluation by the Patient-Centered Outcomes Research Institute which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the research team to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of harm to self or others. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

If you tell us or we learn something that makes us believe that you or others have been or may be harmed, we may be required to report that information to the appropriate agencies.

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the research team your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Alcohol/substance abuse treatment records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the research team or others during or after this study. Examples include:

- The research team may need the information to make sure you can take part in the study.
- The research team may need the information to look for side effects or check your test results.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - o Make sure the study is done safely and properly
    - o Learn more about side effects
    - o Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The research team may need to use the information to create a database of information about your condition or its treatment.
- Information about your study participation may appear in your regular <site> medical record.
- If you receive any payments for taking part in this study, the <site> finance department will need your name and address for tax reporting purposes. In a calendar year if: 1) your payments total greater than $400 for this study or 2) if you receive payments of greater than $400 for being in more than one study, the <site> finance department will also require your Social Security Number for tax reporting purposes. If you do not wish to provide your Social Security Number, you may continue to participate in research studies, but you will not be able to receive payment for the remainder of the calendar year.

- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?
As a rule, the research team will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the <site> Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the <site> "Notice of Privacy Practices". This information is also available on the web at <site URL link>. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?
Your permission will not expire unless you cancel it. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: <name>
Mailing Address: <address>
Telephone: <site phone>
Study Coordinator: <name>
Mailing Address: <address>
Telephone: <phone>

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

<site> Institutional Review Board
<address>
Telephone: <phone>
Fax: <fax>
e-mail: <email>

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the <site> Compliance Help Line at <phone>. *When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRB number (at the top of this form), and details about the problem. This will help officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.*

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular <site> medical record.)*

12. SIGNATURES

Sig-A

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with [NAME OF STUDY TEAM MEMBER OBTAINING CONSENT] _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name:

_____

Signature:

_____

Date of Signature (mm/dd/yy): _____

Sig-D

Consent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable data for use in future research. I understand that it is my choice whether or not to allow future use of my data collected for this project. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____Yes, I agree to let the study team keep my data for future research.

_____No, I do not agree to let the study team keep my data for future research.

Print Legal Name:

_____

Signature:

_____

Date of Signature (mm/dd/yy): _____

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Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES): protocol for a pragmatic, international multicentre randomized trial

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Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES): protocol for a pragmatic, international multicentre randomized trial

Protocol

Mark C Bicket, Karim Shiraz Ladha, Simon Haroutounian, Kellie McFarlin, Mary Neff, Rachel L McDuffie, Jennifer F Waljee, Duminda Nalaka Wijesundera, Chad Brummett, Yi Li, and the CARES Investigators

Correspondence to Dr. Mark C Bicket; mbicket@umich.edu

Abstract

Introduction Acute pain is commonly experienced by millions of patients who undergo outpatient surgical procedures. Moreover, an increasing number of procedures are performed on an outpatient basis, requiring greater postoperative planning to ensure effective pain management. Analgesic approaches commonly involve prescription opioids and non-steroidal anti-inflammatory drugs (NSAIDs), but an optimal regimen that balances pain and adverse effects has not been identified. In addition, critical gaps in evidence exist regarding how opioids and NSAIDs compare as analgesic regimens after surgery.

Methods and analysis The CARES Trial (Comparing Analgesic Regimen Effectiveness and Safety after Surgery) is a pragmatic, international, multicenter randomized trial that enrolls adults undergoing three elective surgical procedures (laparoscopic cholecystectomy, breast lumpectomy, hernia repair). Participants are randomized to receive discharge analgesic prescriptions that consist of either non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose opioids (i.e., 10 pills of oxycodone 5 mg or equivalent), with both groups prescribed acetaminophen around-the-clock. The primary effectiveness outcome is patient-reported worst daily pain intensity over the first seven days after surgery. The primary safety outcome is the occurrence of opioid and/or NSAID side effects over the first seven days after surgery. Secondary outcomes are assessed by patient-report and medical record review at 1 week, 1 month, 3 months, and 6 months after surgery and include sleep disturbance, patient perception of improvement/change after treatment, pain interference, anxiety, depression, health related quality of life, clinically important adverse events, substance use, opioid misuse, chronic pain, healthcare utilization related to pain, and quality of recovery.

Ethics and dissemination Investigational review boards at the University of Michigan and other sites have approved the CARES Trial. The first patient enrolled in CARES in February 2023, with recruitment anticipated through 2026. Dissemination builds on the input of patient partners and other members of an engaged stakeholder advisory board, with activities spanning co-production of summaries to share results with study participants, publications in biomedical journals and lay press, presentations to scientific and community organizations, and other multimedia communication materials.

Trial registration number at clinicaltrials.gov: NCT05722002

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Disclaimer: All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Competing Interests: MCB reports funding from Blue Cross Blue Shield of Michigan unrelated to the current work. SH reports research funding from Eli Lilly, and personal fees from Vertex and Noema Pharma, unrelated to this work. KSL reports consulting fees from Vectura Ferritin Pharma and Merck, unrelated to this work. The other authors report no competing interests.

Author's Contributions: All authors (MCB, KL, SH, KM, MN, RM, JW, DNW, CMB, YL) contributed to the development of the study protocol. The manuscript was drafted by MCB and reviewed and approved by all authors. MCB. is the guarantor.

Strengths and limitations of this study

- The CARES trial (Comparing Analgesic Regimen Effectiveness and Safety after Surgery) examines patient-centered outcomes for two prescription analgesic regimens to treat pain after discharge from common outpatient, elective surgical procedures.
- Key outcomes include patient report of worst pain intensity and medication side effects on a daily basis in the first week after surgery, as well as recovery, health related quality of life, mental health, substance use, and opioid misuse measures up to 6 months after surgery.
- Engagement with Patient Partners and partners from community, professional, and other groups from inception to design, conduct, and eventual dissemination has increased the relevance and impact of results from CARES
- Key outcomes, which include pain and opioid use, rely on patient report and medical record review for ascertainment, and while standardized questionnaires and abstraction approaches are used, events not reported by patients or recorded in health records may be missed.
- The pragmatic design of the study permits participants to address breakthrough pain while recovering at home after surgery by receiving prescriptions for analgesics, which may lead to crossover but mimics real world care.

Introduction

Acute pain after surgery is one of the most common issues confronting patients and surgical care teams. Analgesic regimens to treat pain after discharge from outpatient surgery have commonly relied on opioid medications, with recent emphasis on non-opioid medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. While concerns about opioid prescribing for acute postoperative pain have grown, comparative effectiveness research of different analgesic regimens has not kept pace with modern day practice. Gaps in evidence exist for what constitutes the best analgesic regimen to prescribe patients after discharge from low-risk surgery.

Despite how commonly opioid and NSAID analgesic regimens are prescribed to relieve pain after low-risk surgery, little is known about how these regimens compare regarding the ability to reduce pain in the days that follow surgery. No evidence exists from randomized controlled trials regarding pain relief after surgery for time periods of 1 day or more after low-risk surgery. Additionally, no evidence exists for surgical patients who take these analgesic regimens about short-term side effects, which include nausea and constipation. Concerns also exist regarding the profile of potential side effects and harms that differ for both types of analgesic regimens, such as prescription opioid use with sedation and misuse and NSAIDs with increased bleeding risk. Data suggest that the choice of analgesic regimen may influence quality of recovery, function, and sleep after surgery, but the extent of these effects has not been well characterized for surgical patients.

The Comparing Analgesic Regimen Effectiveness and Safety for surgery (CARES) Trial evaluates multiple patient-centered pain and safety outcomes over 6 months after three of the most common outpatient surgical procedures: laparoscopic cholecystectomy, inguinal hernia repair, and breast lumpectomy. We hypothesize that patients who receive NSAID analgesic regimens will have less acute pain over 7 days after surgery when compared to patients who receive opioid analgesic regimens. Further, we hypothesize that patients who receive NSAID vs. opioid analgesic regimens will have fewer adverse medication-related symptoms and clinically important adverse events, as well as fewer disturbances in sleep over 30 days after surgery. Finally, we hypothesize that patients who receive NSAID vs. opioid analgesic regimens will have better overall quality of recovery, higher pain-related function, and greater health-related quality of life after surgery and will have less chronic pain and experience lower rates of opioid and substance misuse up to 180 days after surgery.

Methods and analysis

Study Design Overview

CARES is a pragmatic parallel arm randomized controlled trial designed to compare the effectiveness of two analgesic prescribing strategies to treat acute pain after discharge from outpatient surgery at 1 week and up to 6 months after surgery. This study compares two flexible prescribing regimens that can each be tailored to individual patient preferences. Patients are assigned to one of two arms, either 1) the NSAID arm, which emphasizes one type of NSAID non-opioid medication taken with acetaminophen, or 2) the opioid arm, which emphasizes the use of one opioid analgesic taken with acetaminophen. CARES randomizes adults undergoing one of three common low-risk surgical procedures, laparoscopic cholecystectomy, inguinal hernia repair, and breast lumpectomy, to either the NSAID or opioid arm using a 1:1 allocation. The intervention structure and data collection protocol is the same for both arms; only the prescribing strategy assignment differs between them. The CARES study group is described in online supplementary materials (Supplemental Appendix) Multiple tradeoffs between pragmatic/effectiveness and explanatory/efficacy trial designs were considered, with a full PRECIS-2 assessment to characterize these choices across 9 domains (Figure 1, Supplemental Exhibit 1).

Recruitment

For inclusion criteria, adults are eligible for participation if they have no significant analgesic medication use before surgery and undergo one of three common outpatient surgical procedures using the following definitions:
(a) No significant analgesic medications before surgery: We define significant use as over-the-counter NSAID use on >7 of 30 past days or prescriptions for analgesic medications before surgery as taking opioid or NSAID medications that are prescribed to the patient in the past 30 days, or prescription before surgery of opioid or NSAID medications by someone other than a member of the surgical team for the purposes of treating pain after discharge from surgery.
(b) One of three common outpatient surgical procedures: The three common low-risk surgical procedures include laparoscopic cholecystectomy, inguinal hernia repair, and breast lumpectomy. These procedures were selected because they are frequently performed (>5000 cases daily in the US) and involve diverse populations.[1]

As a pragmatic trial, this study enrolls a generalizable sample of surgical care patients who would be considered eligible for either NSAID or opioid analgesic therapy. We have therefore kept exclusion criteria to the minimum necessary to ensure both patient safety and internal validity. Adults who meet any of the following exclusion criteria that may interfere with providing informed consent or outcome assessment are ineligible: a) schizophrenia, bipolar disorder, or other psychosis; b) anticipated other surgery within 6 months; and c) anticipated life expectancy of less than 6 months. We also exclude patients with absolute contraindications to either prescribing strategy.

Finally, because participants should be considered eligible in clinical practice for either NSAID or opioid analgesic regimen, patients with contraindications to acetaminophen, study related NSAID drugs, and study related opioid drugs are excluded. In general, contraindications for specific medications include known allergy, liver disease or failure, estimated GFR <60 mL/min, heart failure, peptic ulcer disease, anticoagulation, heart surgery, acute psychiatric instability (defined as current uncontrolled severe depression, severe PTSD, or suicidal ideation), substance use disorder not in remission or treatment, and diversion of controlled substances.

Identifying potential participants

Potentially eligible patients of participating surgeons are identified through local searches of preoperative visits in surgical clinical schedules, anesthesia clinics, and/or local electronic health record searches for eligible patients. Searches are updated at least every month during the enrollment period.

Potentially eligible adults are contacted via phone, patient portal, or in clinic with a recruitment message describing the study. Potential participants may be contacted again within a week after receipt of this message to determine interest in participating and to assess eligibility. If the patient is eligible and interested in participating, a study staff member guides the patient through the screening and informed consent process.

Potential participants are directed to complete a screening survey to determine eligibility for the study (e.g., assess criteria like analgesic use before surgery). Potential participants may opt to either download the MyDataHelps study app for consent and screening, or complete a parallel web version. Research staff provide technical support in downloading the app used for self-administered tools and patient-reported outcomes, and check for completion of surveys. Mobile devices are provided to participants who do not have one, and use a web interface to assess any participants waiting for their device to arrive. After participants provide signed informed consent and authorization, the baseline survey is conducted via the mobile app. A second method of enrollment is in-clinic contact of potential subjects by cross-referencing the potentially eligible list with the clinic and/or surgical schedule for each participating surgeon.

This study is performed at sites where we expect approximately 50-60% of the potentially eligible population for all three procedures to be women. Eligible women and those in under-represented racial and ethnic groups are encouraged to enroll. Initial enrollment targets are anticipated to be balanced across sites, with flexibility to modify targets as the study progresses.

Randomization, Masking and Allocation Concealment

Participants provide informed consent and complete the baseline assessment before surgery. On the day of surgery, patients are randomized to the NSAID or the opioid arm. Randomization is stratified by type of surgery (laparoscopic cholecystectomy, inguinal hernia repair, breast lumpectomy) to assure balanced numbers of participants undergoing each procedure. Randomization occurs in randomly varying block sizes of 2 and 4.

Participants are not masked to treatment arm assignment due to the complexity of the masking process and patient desire to know prescribing strategies. The supervising clinical investigators who implement the interventions also are aware of treatment assignment. To maintain allocation concealment, randomization is conducted centrally using the electronic data capture form that captures the study arm assignment, using an algorithm prepared by the study statistician. Outcome assessors, who are research team members that may facilitate completion of surveys for participants in certain circumstances, are masked to treatment assignment. The masking of outcome assessors and the structured nature of outcome measures are expected to minimize potential biased ascertainment.

Interventions

The analgesic prescribing strategies in this proposal were developed from evidence-based recommendations from analgesic prescribing guidelines and systematic reviews. Each medication has demonstrated efficacy from randomized controlled trials.[2] Both prescribing strategies are operationalized by the surgical team, who provide the intervention in the form of analgesic medications prescribed to the patient, for both arms, on the day of surgery. Importantly, both the NSAID and opioid analgesic prescribing strategies are titrated to clinical response rather than a specific type, duration, or dose of treatment. This pragmatic treat-to-target approach more closely mirrors real-world practice, which tailors evidence-based treatments to patient-specific outcomes.

The NSAID analgesic prescribing strategy includes prescriptions by the surgical team for one non-steroidal anti-inflammatory drug and acetaminophen. For the NSAID prescription, the surgical team may choose among one of the following three options:

- *Ibuprofen 600 mg by mouth every six hours around the clock for three days, then as needed for pain thereafter (total #10 doses)*
- *Celecoxib 400 mg by mouth once then 200 mg every twelve hours around the clock for three days, then as needed for pain thereafter (total #10 doses)*
- *Naproxen 500 mg by mouth once then 250 mg every eight hours around the clock for three days, then as needed for pain thereafter (total #10 doses)*

The opioid analgesic prescribing strategy includes prescriptions by the surgical team for one opioid medication and acetaminophen. For the opioid prescription, the surgical team may choose to prescribe among one of the following three options, which are similar in opioid potency by morphine milligram equivalents:

- *Oxycodone 5 mg by mouth every four to six hours as needed for pain (total #10 doses)*
- *Morphine 7.5 mg by mouth every four to six hours as needed for pain (total #10 doses)*

- *Hydromorphone 2 mg by mouth every four to six hours as needed for pain (total #10 doses)*

For participants in both arms, the surgical team prescribes acetaminophen 1000 mg by mouth every 6 hours around the clock for the first three days after surgery then as needed thereafter (total #20 doses). Participants experiencing poor pain control will be encouraged to contact their surgical team. Participants may receive additional pain treatments at the direction of their surgical team, including additional doses of medications in line with their study arms. For example, additional doses of NSAIDs may occur in the NSAID arm (maximum doses of ibuprofen 3200 mg, naproxen 1500 mg, celecoxib 800 mg). Additional doses of opioids may also take place in the opioid arm. If needed, crossover to medications from the other study arm will be permitted.

Medication safety considerations

Participants are informed of potential interactions and safety considerations, in line with standard of care, at the time of analgesic regimen prescribing. At study assessments, use of study medications and over-the-counter medications is evaluated. Participants receive closer monitoring than is available in usual practice. The study permits other aspects of perioperative and surgical care per the usual practices of surgical teams and does not specifically direct the use of local anesthetics provided by the surgical team in the operating room

Recommendations for prevention of constipation are provided to participants in both study arms at the outset as per the usual practice at each study site. Important adverse events (e.g., bleeding) are evaluated by a study physician and reported to the patient's surgical provider. Potentially urgent adverse events (e.g., chest pain) are referred for immediate evaluation in the local clinic or emergency department.

Data Collection

Study measures include both patient-reported measures that are collected in assessments at baseline and as outcomes in the time period after surgery. Assessments require approximately 25 minutes at baseline, 3 months, and 6 months; and approximately 15 minutes at 1 week and 1 month. A small, graded incentive (in increments increasing from USD$10 to USD$15, totaling USD$80 for completion of all surveys in the study period) is provided for each outcome assessment. Incentives of this magnitude offset costs of participation and are in the standard range used in our previous studies. No incentives are provided for daily monitoring of pain and analgesic use, which is conducted for clinical intervention purposes.

Patient-reported outcome measures and timing of administration are displayed in Table 1. Although participants are asked to complete a substantial battery of patient-reported measures in this proposed study, we perceive this outcome assessment protocol to be both appropriately comprehensive and reasonable in terms of respondent burden, and patient partners supported this approach to assessment. Outcome assessment protocols of similar length have been well tolerated in multiple previous symptom management trials involving patients with pain after surgery. Participants in these trials have also reported that they appreciated the sustained attention to their symptoms and perceived benefit from therapeutic disclosure.

Table 1: Patient-reported Outcome Assessment Schedule

Domain	Measure	Schedule					
		BL	D 1-7	1 wk	1 mo	3 mo	6 mo
Pain	Brief Pain Inventory short form surgical site worst pain	X	X	X	X		X

	PROMIS Pain interference	X				X	
	Global Rating of Change			X	X		
	Analgesic use		X	X	X	X	X
	Acute pain body map	X	X	X	X	X	
	Brief Pain Inventory short form whole body worst pain	X			X	X	X
	Chronic pain body map and symptom severity index	X				X	X
	Other postoperative pain treatments		X	X			
Adverse Effects	Symptom checklist	X	X	X	X		
	PROMIS Sleep Disturbance	X			X		
Recovery	Quality of recovery		D3	X			
Health-related quality of life	PROMIS Fatigue	X		X	X	X	
	PROMIS Cognitive Function	X		X	X	X	
	PROMIS Social Roles	X		X	X	X	
	PROMIS Physical Function	X		X	X	X	
Mental Health	PROMIS Depression	X					
	PROMIS Anxiety	X					
	Pain Catastrophizing Scale	X					
Substance use	TAPS	X				X	X
	Opioid misuse	X				X	X
	New prolonged opioid use						X
Other	Healthcare utilization				X		X

Notes: Baseline (BL), D (Day), Patient Reported Outcomes Measurement Information System (PROMIS), Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool.

Description of patient-reported outcomes

National guidelines for the conduct of pain clinical trials recommend assessment of core outcome domains such as pain intensity and function, global improvement, symptoms, and adverse events.[3] Each of these pain outcome domains is assessed with validated patient-reported measures.

1. The Primary effectiveness outcome for Aim 1 is acute postoperative pain over 7 days at the site of surgery. The Brief Pain Inventory (BPI) pain intensity score is used as the primary measure of pain intensity for acute pain over the first 7 days. BPI is also used to measure chronic pain at 180 days. Specifically, the BPI worst pain intensity, which is a 0-10 item, assesses worst pain intensity in the past 24 hours. The BPI was originally developed for use in cancer-related pain, but has been validated for use in numerous other populations, including acute pain after surgery.[4] As the primary effectiveness outcome, this is assessed over the first week after surgery. The BPI worst pain score is also used to measure whole body pain.

2. The primary safety outcome for Aim 2 is adverse medication-related symptoms. An adverse effects Symptom Checklist proactively screens patients for their report of adverse events from analgesic medications over the first 7 days after randomization, in line with pain clinical trial guidelines (**Table 2**).[5] The validated Symptom Checklist assesses the number and severity of common symptoms.[6] The list was adapted to include the most common side effects from NSAID and opioid oral analgesics for postoperative pain identified in a Cochrane review.[7] The instrument can be completed in <3 minutes. The primary safety outcome is the presence of any

adverse medication-related symptoms over the first 7 days of surgery because the vast majority of patients complete analgesic use after for the procedures included in CARES by this time.

Table 2. Postoperative adverse medication-related symptoms for the CARES Trial.

Have you experienced any of these symptoms today? Select all that apply.

☐ Nausea	☐ Vomiting
☐ Constipation	☐ Diarrhea
☐ Itching (pruritus)	☐ None

Have you experienced any of these symptoms today? Select all that apply.

☐ Stomach pain	☐ Difficulty sleeping (insomnia)
☐ Heartburn	☐ Generalized weakness (asthenia)
☐ Gas	☐ Tiredness
☐ Headache	☐ Drowsiness or sleepiness (somnolence)
☐ Lightheadedness	☐ Sweating
☐ Dizziness	☐ Flushing
☐ Runny nose	☐ Rash
☐ Dry mouth	☐ Fatigue
☐ Confusion	☐ Difficulty passing urine
☐ Difficulty concentrating	☐ None

Any other symptoms you want to report _____

Symptoms can be classified as:
Mild = you notice symptoms, but they aren't a problem
Moderate = symptoms that limit of your normal daily activities
Severe = symptoms make normal daily activities difficult or impossible

For each symptom checked, user then select from the following options:
☐ Mild ☐ Moderate ☐ Severe

Notes: Adapted from the Medication Symptom checklist and Moore et al.[6,7]

3. Secondary outcomes include measures for other pertinent domains. PROMIS Pain Interference scale (SF-6a) is a validated and reliable instrument that can be completed in <2 minutes to measure pain-related function.[8–11] A 7-grade patient-reported global impression of change rating assesses patients' views of overall improvement or worsening pain.[12] Analgesic use includes assessment for the analgesic prescriptions written by the surgical team via chart review and patient-reported medication use (pills consumed [NSAID, opioid, acetaminophen], any other pain treatments). This permits an examination of adherence to the study regimen and potential crossover to the other study arm. A checklist of other postoperative pain treatments adapted from the Michigan Surgical Quality Collaborative will assess for non-prescribed treatments for pain after surgery such as ice, heat, and cannabis (**Table 3**).[13,14]

Table 3. CARES measure on other postoperative pain treatments

For Baseline: Do you currently use any of the following ways to reduce your pain? Select all that apply. If you have no pain, select "none"

For Postoperative Days 0-7: Have you used any of the following ways to reduce your pain at the site of surgery in <the past 24 hours; other time period>? Select all that apply.

☐ Ice/cold packs or cryotherapy	☐ Watching TV/movies, reading, music
☐ Marijuana, cannabis, or CBD	☐ Meditation, deep breathing
☐ Heat packs	☐ Electrical stimulation, TENS
☐ Massage	☐ Prayer
☐ Topical drugs like Icy Hot or Salonpas	☐ Talking to others
☐ Acupuncture, acupressure	☐ Other
☐ Exercise, yoga, or walking	☐ None
Other approach to reducing pain _____ (free text)	

Notes: Responses include options based on the Michigan Surgical Quality Collaborative postoperative survey, Komann, et al., and Fan et al.[13,14]

The Michigan Body Map has been validated to measure areas of chronic pain over the body. This will include questions on the symptom severity index (SSI) to enable calculation of a score representative of widespread body pain.[15,16] The Michigan Body Map will also be adapted to measure locations of acute pain over the body that may be outside the site of surgery. PROMIS Sleep Disturbance v1.0 has been validated as 4 items measuring sleep problems.[17,18] Quality of recovery is assessed via the internationally validated Quality of Recovery-15 score, which details five domains about how well a person recovers after surgery.[19,20] PROMIS Preference score (PROMIS 29+2 Profile v2.1) is a health-related quality of life measure that has demonstrated validity.[21] It provides PROMIS scores for Cognition (Cognitive Function and Cognitive Function Abilities), Depression, Fatigue, Physical Function, Ability to Participate in Social Roles/Activities, as well as Pain Interference (4a) and Sleep Disturbance. PROMIS Anxiety includes 4 questions about anxiety. The Tobacco, Alcohol, Prescription medications, and other Substance (TAPS) Tool consists of a 4-item screening for tobacco use, alcohol use, prescription medication misuse, and illicit substance use in the past year and brief assessment.[22,23] One question from the National Survey on Drug Use and Health (NSDUH), a national survey with established validity and reliability, assesses for opioid misuse defined as use that is more than prescribed, for non-pain-related reasons, or in a way not prescribed by a doctor.[24,25] New prolonged opioid use, defined as filling ≥1 opioid prescription post-discharge between 4 and 90 days and also between 91 and 180 days, will be assessed by patient report.[26] Patients will also be asked to report on healthcare utilization at 1 and 6 months after surgery, including unplanned postoperative clinical interactions related to pain (patient messages, phone calls, non-routine clinic visits related to pain), emergency room visits, and hospitalizations.

Description of other measures

At baseline, patients complete questions on demographics,[27–33] a comorbidity checklist derived from the Charlson index,[34] treatment expectations (**Table 4**), depression (PHQ-2),[35] anxiety (GAD-2),[36] the pain catastrophizing scale (PCS short from 6),[37] and preference on the return of study results. The local study team reviews a patient's chart to examine for characteristics of the perioperative period, procedure, and PACU course. The local study team reviews a participant's chart to assess for clinically important adverse events at the

end of the study period. This review also assesses for unplanned postoperative clinical interactions related to pain including patient messages, phone calls, non-routine clinic visits related to pain. This also assesses for emergency room visits, hospitalizations, and 30-day complications after discharge measured using the American College of Surgeons' (ACS) National Surgical Quality Improvement Program (NSQIP) definitions.[38]

The central study team assesses new prolonged opioid use by obtaining prescription drug monitoring program data, if available. Data necessary for linkage includes name (first, last), date of birth (month/day/year), and gender.

Table 4. CARES measure on expectations prior to surgery

Statement or Question	Responses
Please indicate your expectations regarding your surgery and health care team, using a 0 to 10 scale, for the following items. *(Randomize list)*	-
1. How much functional ability do you expect to have after you recover from surgery?	0=expect no ability (maximum impairment), 10=expect to be fully functional
2. I expect that the pain related with this surgery will relieve over time.	0=expect no pain relief, 10=expect full pain relief
3. I'm afraid of pain or other complications during and/or after surgery.	0= not at all afraid, 10=extremely afraid
4. Please rate how much pain you expect to have by circling the one number that best describes your expected pain on the first day after you recover from surgery.	0=expect no pain, 10=expect pain as bad as you can imagine
5. Please rate how much pain you expect to have by circling the one number that best describes your expected pain at one month after you recover from surgery.	0=expect no pain, 10=expect pain as bad as you can imagine
6. I expect that the pain related with this surgery will be relieved by taking prescription strength non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib, or naproxen.	0=expect no pain relief, 10=expect full pain relief
7. I expect that the pain related with this surgery will be relieved by taking prescription strength opioid drugs such as oxycodone, morphine, or hydromorphone.	0=expect no pain relief, 10=expect full pain relief
8. I expect to experience side effects from prescription strength non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib, or naproxen that I take to relieve pain after surgery.	0=expect no side effects, 10=expect side effects as bad as you can imagine
9. I expect to experience side effects from prescription strength opioid drugs such as oxycodone, morphine, or hydromorphone that I take to relieve pain after surgery.	0=expect no side effects, 10=expect side effects as bad as you can imagine
10. What treatment group do you prefer to be in?	NSAIDs, Opioids, No preference

Trial Data Sources

A mature and integrated digital informatics infrastructure is employed in CARES using CareEvolution MyDataHelps. Data gathered by patient report via the study app MyDataHelps

participant portal is integrated into the trial data. Research participants consent using the app, complete patient reported outcome measures, and receive return of results. If patients do not have a mobile device, they may use a study participant portal to complete patient-reported outcomes. As a final step to ensure complete follow up, research coordinators may contact patients to assist with completion of participant provided information if necessary. Sites use MyDataHelps to document patient screening, approach, consenting, and enrollment using electronic case report forms (eCRFs). MyDataHelps includes customizable, data-driven eCRFs to capture data gathered by research coordinators at each site. Standardized data forms capture data from the perioperative period including immediately before, during, and after surgery. MyDataHelps has been used to document clinical quality projects and prospective observational research, and has met strict medicolegal, audit trail, electronic signature, and disaster recovery requirements across federal and state regulations.

Prevention of Missing Data

In pain clinical studies, dropouts often occur due to intervention-related factors (e.g., adverse effects, lack of treatment efficacy) and missing data can pose a substantial threat to internal validity. CARES has several design features meant to enhance participant retention and reduce missing data. First, the interventions are flexible treat-to-target analgesic prescribing strategies that allow tailoring to each type of procedure for patients. Second, both study arms are active interventions, which should reduce differential dropout that can occur among patients assigned to a control arm. Third, randomized participants are strongly encouraged to complete all outcome assessments, and individuals who do not respond to the study app assessment receive in-app reminders and phone call reminders from study staff. Fourth, to reinforce participants' sense of commitment to the study, participants receive quarterly CARES newsletter including tips on pain management and positive news related to recovery from surgery. Finally, if participants are at risk of dropping out due to assessment burden, they are given the option of completing a minimum core assessment comprising primary pain (i.e., BPI) and adverse effect (e.g., symptom checklist) measures.

Sample Size and Power

The sample size for CARES was calculated based on testing the superiority of NSAID versus OPIOID analgesic regimens on effectiveness for acute pain. Because the surgical community has considered pain and post-discharge prescribing guidelines in the context of specific types of surgical procedures, the trial is powered to test the superiority for each one of the three types of low-risk surgeries included in CARES (i.e., gallbladder removal, inguinal hernia repair, breast lumpectomy).[39–43] To account for multiple comparisons, a two-sided Type I error of 0.016 after applying a Bonferroni correction was used to control the family-wise error rate of 0.05 with three procedure types. Also, 90% power testing was used for superiority (two-sample t test) at the Day 7 assessment, but achieved power in the GEE models will be improved by the repeated outcome measures. The outcome measure for BPI pain intensity has a mean of ~3.4 (standard deviation of 2.1) in prior samples of low-risk surgical patients, and past studies suggest a difference of 1.0 represents a minimally important difference.[44–46]

For the superiority analysis, calculations in Stata estimated that 244 patients (or 122 per arm with 1:1 allocation ratio) were required to detect a difference in means of >=1. Based on prior work, we conservatively assume a 15% f or loss to follow up. This requires enrolling 288 patients per type of surgery. To account for the three types of surgery, the study anticipates recruiting a total study population of 900 (300 patients per type of surgery).

The CARES Study is also powered to examine heterogeneity of treatment effects and detect differences for subgroup analyses. After testing for effect modification, tests for examining outcomes among a priori selected subgroups will occur based on differences in acute pain, opioid prescribing, and access to pain care.[41,43,47] These subgroups include: (1)

male/female patients; (2) age <65/>=65 years; (3) black/white patients; and (4) urban/rural patients. We calculated power for the effectiveness of subgroups, using the total study population and Bonferroni adjustment for 8 prespecified comparisons (2 each for sex, age, race/ethnicity, and urban/rural, with P values <0.00625). We anticipate the smallest subgroup size to be >=15% of the total sample.

Data and Safety Monitoring

The study team formalized the data safety monitoring plan and formed an independent data safety monitoring board (DSMB) for CARES in consultation with the funder. The CARES DSMB provides independent review of the study to ensure the safety of participants and the validity and integrity of the data. Its members include relevant context experts (e.g., surgeon, anesthesiologist, biostatistician with clinical trials experience, Patient Partner, et al.) and a DSMB Chair. The CARES DSMB charter was written and approved by concerned parties. The CARES DSMB meets two to three times per year.

Plans include for data by treatment group to be seen by the CARES DSMB after enrollment of the first 100 patients, and after 25%, 50% and 75% accrual of the sample; the CARES DSMB has sufficient data to assess data integrity and to compare rates of adverse events between treatment arms that may raise safety concerns. The CARES DSMB may consider termination at any point based on unexpected safety findings; however, early stopping criteria are not planned due to apparent benefit since neither approach is experimental, both approaches are widely used, and because substantial evidence from an adequately powered trial is needed to affect clinical practice. The initial CARES DSMB meeting focused on review and approval of the study protocol and its informed consent template. Thereafter, the CARES DSMB reviews primary and secondary safety outcome data, data quality, enrollment data and projections.

Patient and public involvement

We have engaged and will continue to engage with patient partners, who are patients or caregivers with lived experience with each of the three included types of procedures as well as being prescribed and using one or more of the study medications for pain relief. We have also engaged with other important stakeholders to develop CARES for several years using a variety of approaches. We conducted a patient-preference survey among 42 persons before surgery, which indicated that 71% would join the study and be randomized.[48] Survey results also informed the study design, in that many respondents indicated reticence in participating in the study were their analgesic regimen to be masked. In partnership with the Michigan Institute for Clinical and Health Research, we convened a Community Engagement Studio to share a synopsis of the study protocol and learn the perspectives of twelve Patients with Lived Experience. In the studio, patients offered feedback regarding the primary and secondary outcomes for the study, including identifying two outcomes of key importance (pain intensity, adverse events), as well as the recruitment strategy and factors regarding whether they would participate. Further, one of the CARES study co-investigators has experience as a caregiver and leader involved in relevant community organizations.

CARES also engages with patient and public members by convening a Stakeholder Advisory Board that includes five patients partners who include patients with lived experience and seven non-patient stakeholders. The CARES Stakeholder Advisory Board meets three to four times per year, where members offer perspectives and feedback that have informed the design and conduct of the study, and informs the dissemination of results. For example, Patient Partners and members of the Stakeholder Advisory Board reaffirmed and clarified the primary effectiveness and safety outcomes for the CARES Trial. Patient Partners identified worst pain after surgery, pain happening on the earliest postoperative days (i.e., postoperative day 1 or 2), and side effects from pain medications as among the most important and relevant outcomes

based on their experiences. In collaboration with our Patient Partners and other stakeholders, priority was given to the following questions faced by surgical patients requiring prescription medications to treat pain: (1) Will the analgesic regimen that I receive adequately relieve my acute pain as I recover from my surgery? (2) Will my analgesic regimen influence my risk of experiencing an adverse effect as I recover from my surgery? And (3) Will my analgesic regimen influence the quality of my recovery, my ability to function free of pain, my quality of life, my risk of experiencing chronic pain, and my risk of either misusing opioid medications or using other substances? Patient partners and stakeholders also helped to select additional measures based on patient-centeredness, validity, reliability, sensitivity, and brevity, with focus on reducing patient burden.

Collaboration with the Stakeholder Advisory Board including Patient Partners includes framing results from the CARES Trial in ways that are understandable and impactful to the millions of patients who undergo low-risk outpatient surgeries every year. Co-production of three types of content and content summaries for the CARES Trial is planned, which include lay language text summaries of overall study findings, contextual text summaries that include insights relevant to different study subgroups, and digital multimedia summaries that use video, audio, and other media.

Ethics and Dissemination

The CARES trial Institutional review boards at participating sites have approved the CARES trial, including the University of Michigan Institutional Review Board (IRBMED HUM00215416). The first patient was recruited in February 2023. Enrollment is anticipated to continue until 2026. A model consent form is provided in supplemental material Exhibit 2.

CARES Trial results have significant potential for reproduction, dissemination, and implementation across the U.S and Canada. The CARES Trial proposal has been carefully designed to include characteristics that maximize the ability to replicate study findings and put findings into practice in diverse care settings. The two comparators of NSAID and opioid analgesic regimens represent readily available medications already in widespread use as prescribed by surgeons to patients after low-risk outpatient surgery. The flexibility built into the two regimens increases their ability to be used by more patients and in more care settings. By including three different types of low-risk surgery and focusing on four different types of patient subgroups, the ability to apply this work to varied types of surgery and groups of patients is enhanced.

Unique opportunities exist to disseminate findings from the CARES Trial beyond traditional academic venues. Existing infrastructure includes the Overdose Prevention Engagement Network (OPEN) to support dissemination activities.[49] Past evidence of OPEN dissemination includes reference for guidelines by federal entities including the Centers for Disease Control and Prevention and national quality organizations including the Leapfrog Group.[50] OPEN meets with various stakeholders within the state of Michigan and across the nation, and these meetings serve as an additional mechanism to disseminate this work. Through the Institute for Healthcare Policy and Innovation (IHPI) at the University of Michigan, a robust team of liaisons engage with Federal and state legislators, and dissemination will continue through one-on-one meetings and organized events coordinated by these channels. The Stakeholder Advisory board will help design digital multimedia communication materials and share information through events relevant to broader communities. Partnership with the Michigan Surgical Quality Collaborative, which engages with all major hospitals across Michigan, and Blue Cross Blue Shield of Michigan, is planned to disseminate study findings from the CARES Trial, similar to our previous work in reducing opioid prescribing while maintaining patient-reported outcomes.[51–53]

Consideration for possible barriers to disseminating and implementing the results from the CARES Trial has been given. Some patients may hesitate to accept findings favoring either

NSAID or opioid regimens, due to the personal nature of pain. To address this issue, data elements include patient-reported outcomes for pain, adverse events, and important secondary outcomes after surgery. Examination of how well and how safe these regimens work in diverse groups of patients is planned, as well as collaboration with the Stakeholder Advisory Board including Patient Partners in order to frame results from the CARES Trial in ways that are understandable and impactful to the millions of patients who undergo these low-risk outpatient surgeries every year. Surgical providers may hesitate to adopt findings from CARES for low-risk procedures and only adopt findings for certain types of procedures; for this reason, CARES includes three types of low-risk procedures that vary by important patient characteristics such as age, sex, and body region. CARES Trial findings for NSAIDs vs. opioid may differ among key patient subgroups, type of procedure, or other important features, which may disallow for one consistent message about which analgesic regimen is best. If this happens, the study will adapt messaging and tailor results for each group to align with evidence from the trial.

Conclusion

The CARES Trial is a pragmatic randomized controlled trial that enrolls adults who undergo three common outpatient surgical procedures in order to compare NSAID versus low-dose opioid analgesic regimens with respect to pain, adverse effects, and other significant patient-centered outcomes. By leveraging the expertise of an engaged stakeholder advisory board, as well as diverse recruitment settings that span academic and community health systems, the CARES trial will generate critical evidence to help determine the best post-discharge analgesic regimen that maximizes pain relief while minimizing adverse effects for millions of patients who undergo these procedures every year.

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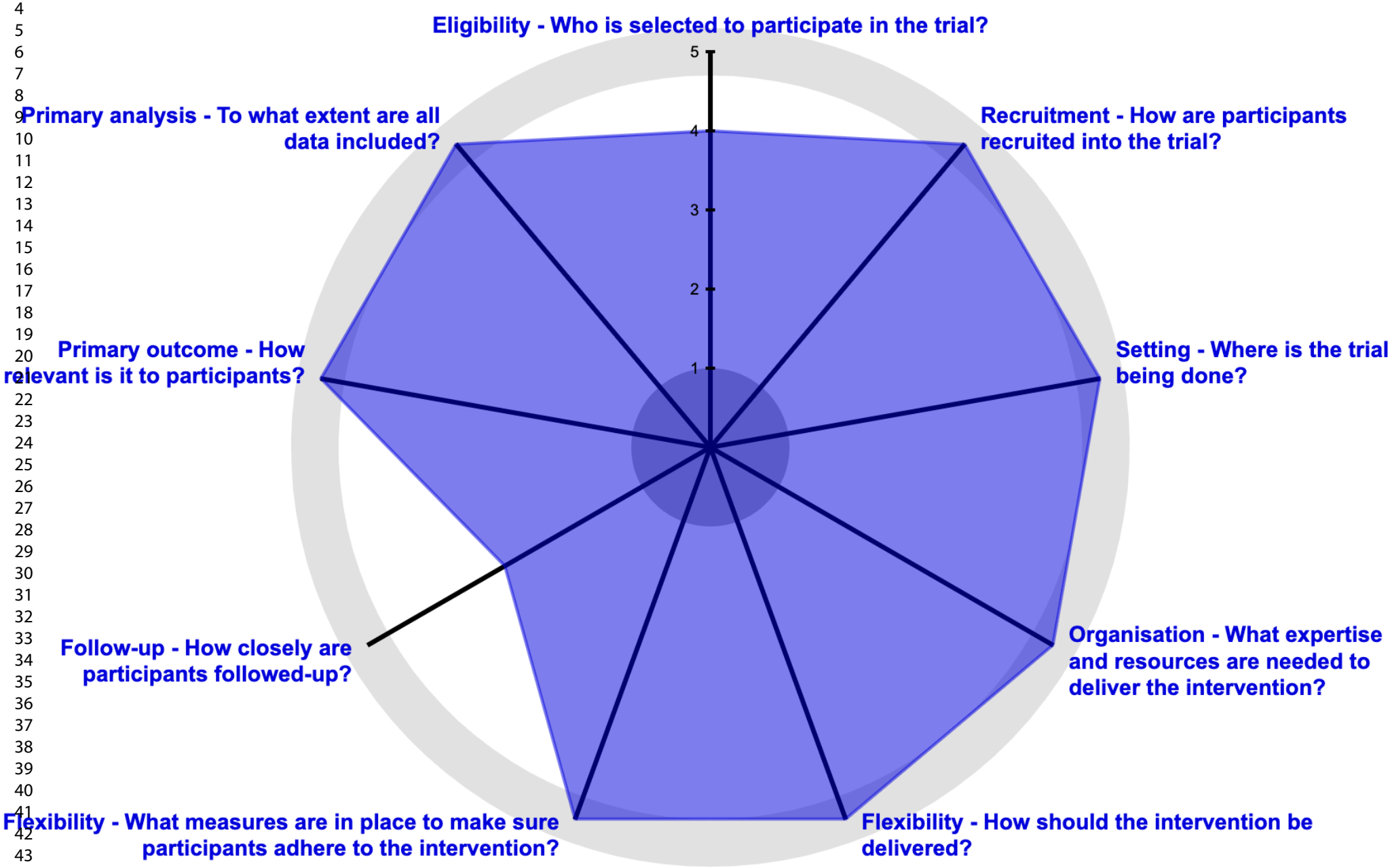
Figure 1. CARES Trial PRECIS-2 Wheel.

Figure 1 Legend: Nine listed domains for the Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) study and the PRECIS-2 Wheel are described in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.



Appendix: Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) Investigator Group
January 2025

CARES Research Team
Principal Investigators:
Mark Bicket, MD, PhD (Principal Investigator), University of Michigan, Ann Arbor, MI
Karim Ladha, MD, MSc, University of Toronto

Co-Investigators:
Chad Brummett, MD, University of Michigan
Simon Haroutounian, PhD, Washington University in St. Louis
Yi Li, PhD, University of Michigan
Kellie McFarlin, MD, Henry Ford Health System
Mary Neff, CRNA, University of Michigan
Jennifer Waljee, MD, MPH, MS, University of Michigan
Duminda N. Wijeysundera, MD, PhD, University of Toronto

Data Coordinating Personnel:
University of Michigan, Ann Arbor, MI
Sarah Clark, BA (Project Manager)
Kendall Dubois, MS (Project Manager)
Alicia Sudayam, BS (Engagement Coordinator)
Vidhya Gunaseelan, MBA, MS, MHA (Lead Data Analyst)
Chiao-Li Chan, MSW (Data Analyst)

CARES Sites
Henry Ford Hospital, Detroit, MI
Principal Investigator: Kellie McFarlin, MD
Site Coordinator: Daniel Molitor, Olivia Dionisio

Washington University St. Louis, St. Louis, MO
Principal Investigator: Simon Haroutounian, PhD
Site Coordinator: Justin Stout, MS

Unity Health Toronto, Toronto, ON, Canada
Principal Investigator: Karim Ladha, MD, MSc
Co-Investigator: Duminda N. Wijeysundera, MD PhD
Site Coordinators: Zaaria Thomas, BA; Roshni Nayar, BSc; Janneth Pazmino-Canizares, MSc; Tedros Mokonnen, BSc

Temple University, Philadelphia, PA
Principal Investigator: Ellen Hauck, MD
Site Coordinator: Adam Lloyd-Jones, BA

Cooper University, Cooper, NJ
Principal Investigator: Wray Hughes, MD
Co-Investigators: Ludmil Mitrev, MD; Lawrence Mulligan, MD

CARES Surgeons
University of Michigan, Ann Arbor, MI

Bess Connors, MD; Justin Dimick, MD, MPH; Lesly Dossett, MD, MPH; Jonathan F. Finks, MD; Tasha Hughes, MD, MPH; Desmond Tuan-Khai Huynh, MD; Grace J. Kim, MD; Nabeel Robert Obeid, MD; Melissa Louise Pilewski, MD; Jenny Meng Shao Kashmanian, MD; Dana Telem, MD, MPH

Henry Ford Hospital, Detroit, MI
Kellie McFarlin, MD; Anthony Falvo, DO; Sina Khoshbin, MD, Kurt Kravalovich MD, Marianne Franco MD, Matthew Madion MD, Abbas Al-Kurd MD, Srinivas Bhandakar MD, Christopher Steffes MD, Oliver Varban MD, Robert Elkus MD

Washington University St. Louis, St. Louis, MO
Rebecca Aft, MD, PhD; Michael M. Awad, MD, PhD; Jeffrey Blatnik, MD; Michael Brunt, MD; Katherine Glover-Collins, MD, PhD; Arnab Majumder, MD; Julie Margenthaler, MD; John A. Olson, Jr., MD, PhD

Unity Health Toronto, Toronto, ON, Canada
Ralph George, MD; David Gomez Jaramillo, MD, PhD; Joao Rezende-Neto, MD, PhD; Jory Simpson, MD, MEd; Brent Hopkins, MD; Morgan Schellenberg, MD; Anna Dare, MD PhD; Najma Ahmed, MD; James Jung, MD PhD

Temple University, Philadelphia, PA
Jessica H. Beard, MD, MPH; Elizabeth D. Dauer, MD; Christina Jacovides, MD; Neil A. King, MD; Zoe Maher, MD; Cristina L. Novak, MD; Abhijit Pathak, MD, MS; Matthew Philp, MD; Mary T. Pronovost, MD; Thomas Santora, MD; Rohit Soans, MD

Cooper University, Cooper, NJ
Umur Atabek, MD; Maureen Moore, MD; Robert Simons, MD

CARES Stakeholder Advisory Board
Lead Stakeholder:
Rachel L. McDuffie, MPH, JD

CARES Patient Partners:
Deidre Bauer
Louis Daher
Carl Henscie
Elizabeth Racz

CARES Stakeholders:
Kanzoni Asabigi, MD, Detroit Area Mental Health Leadership Team
James Grant, MD, Blue Cross Blue Shield of Michigan
Tasha Hughes, MD, Breast Surgeon
Clifford Ko, MD, American College of Surgeons
Gregory Terman, MD, US Association for the Study of Pain

CARES DSMB:
Christopher Wu, MD, (Chair) Hospital for Special Surgery, New York, NY
Michael Smith, PharmD, (Vice Chair) The University of Michigan, Ann Arbor, MI
Gail Einhaus (patient representative), Ann Arbor, MI
Ed Mariano, MD, MAS, Stanford University, Stanford, CA
Blair Richards, MPH, The University of Michigan, Ann Arbor, MI

Supplemental Material for

Bicket MC, Ladha K, Haroutounian S, McFarlin K, Neff M, McDuffie R, Waljee J, Wijesundera DN, Brummett CM, Li Y. Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES): protocol for a pragmatic, international multicentre randomized trial. BMJ Open. 2025

NCT05722002

Supplemental Exhibit 1. PRECIS-2 assessment for the CARES trial.

Supplemental Exhibit 2. Model consent form for CARES trial.

Supplemental Exhibit 1. PRECIS-2 assessment for the CARES trial.

Domain	Assessment
1. Participant eligibility	Since this study will enroll all patients without contraindications to opioids, NSAIDs, or acetaminophen having a surgery of interest across 4 diverse academic and community sites across the US, it is highly pragmatic in this domain.
2. Participant recruitment	Recruitment will take place in usual care settings so that people are recruited after they present to surgery clinics to have a surgery of interest and will draw from multiple clinical sites as an explicit way of increasing applicability of trial results. The study is extremely pragmatic in this domain.
3. Care setting	This study setting will include identical settings to the usual care setting for the analgesic regimen interventions, and include surgery clinics at multiple academic and community sites that treat a patient sample with socioeconomic and ethnic diversity. The study is maximally pragmatic in this domain.
4. Organization resources, expertise, and care delivery	The study includes the prescription of analgesic regimen interventions within the usual organization of care for surgical patients and requires no extra clinicians, training, or expertise to deliver the interventions. The study is maximally pragmatic in this domain.
5. Flexibility of intervention delivery	Treating surgeons and surgical providers will receive brief, simple, and flexible care protocols for patients randomized to analgesic regimens after surgery; these protocols will state explicitly that co-interventions will be permitted based on clinical judgment. The study is maximally pragmatic in this domain.
6. Flexibility of adherence for participants	Treating surgeons and surgical providers will receive brief, simple, and flexible care protocols for patients randomized to analgesic regimens after surgery; use of the analgesic regimen interventions will be measured but not enforced and patients may receive alternative treatments if needed. The study is maximally pragmatic in this domain.
7. Follow-up intensity	Follow-up will occur via a patient-reported smartphone app over 1 week, then 1-, 3-, and 6-months after surgery. Opioid use will be assessed by searches of prescription drug monitoring program data. The study is moderately pragmatic in this domain.
8. Relevance of primary outcome	The primary outcome (pain intensity after surgery at 1 week) is simple and pragmatic; secondary outcomes are also pragmatic endpoints, including side effects, quality of recovery, pain interference, and opioid use.
9. Analysis of primary outcome	All randomized patients will be included in the primary analysis. A priori subgroups will be examined, and adjusted for compliance with the study protocol will only occur in additional analyses. The proposal is highly pragmatic in this regard.

Notes: Nine listed domains for the Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) study and the PRECIS-2 Wheel are characterized in relation to design aspects common to pragmatic (effectiveness) vs. explanatory (efficacy) trials.

Supplemental Exhibit 2. Model consent form for CARES trial.

<SITE> CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: Comparing Analgesic Regimen Effectiveness and Safety for surgery (CARES) Trial

Company or agency funding the study: Patient-Centered Outcomes Research Institute

Principal Investigator: <name>
Study Coordinator: <name>

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the research team about the study and ask them any questions you have.

You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctors. Research studies hope to learn new information about how safe and effective treatments are. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies also have different kinds of risks and risk levels, depending on the type of the study. Some studies do not offer the possibility of receiving treatment, while other studies do. You may also need to think about other requirements for being in this study. For example, some studies require you to answer questions related to your health over several weeks or months. This may require you to change your schedule, find time in your day to respond, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

Pain is a common experience after surgery. Clinicians (like your surgeon) usually choose between two strong pain relievers when prescribing medicine to take home to treat this pain.

We know that both options are effective at treating pain. These options are used every day across the United States by individuals who have the same type of surgery that you will be having. These options are:

Option 1	Option 2
A prescription for non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (Tylenol) Examples of NSAIDs: Ibuprofen, naproxen, celecoxib	A prescription for low-dose opioids and acetaminophen (Tylenol) Examples of opioids: oxycodone, morphine, hydromorphone

This study will compare these two commonly used types of medication. We know that each option works well to manage pain after surgery, but we do not know how they compare to one another. Persons who join the study will receive a prescription for one of these two options. If you join the study, you will decide whether to take the pain medication and, if you do, how much to take. If the medication is not helping to manage pain at home after surgery, you may contact your surgical team and receive any additional treatments they think are appropriate.

Just like all medications, both options may lead to side effects. NSAIDs may cause heartburn, headache, or drowsiness. Opioids may cause sedation, dizziness, nausea, or constipation. Both types of medications could also result in other side effects.

The goal of this study is to answer two key questions faced by patients who need pain medication while recovering after surgery:

- Which option is better at relieving my acute pain?
- Which option lowers my risk of experiencing a side effect?

If you join the study, on the day of your surgery you will be assigned to receive one of the two pain medications options above. You will complete a series of surveys that tell us how well the medication relieves pain, report any side effects, and share how you are recovering after surgery. The research team will also review your health and prescribing records to learn more about how well you recover. The expectation is to have a de-identified dataset at the conclusion of the study.

Randomization: This study involves a process called randomization. This means that the medication to treat your pain after surgery will not be chosen by you or the research team. If you join the study, you will be assigned by chance, like the flip of a coin, to one of the two groups. If you join the study, you need to be comfortable with the possibility of receiving either type of medication to treat your pain after surgery.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include poor pain control or discomfort with study questions. More detailed information will be provided later in this document.

This study may not offer any benefit to you now but may benefit others in the future by determining the best way to treat pain after surgery. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be six months.

You can decide not to be in this study. Alternatives to joining this study include not joining this study or joining a different study. Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Pain after surgery is common, and two types of pain relievers provide very good pain relief after surgery. One option is to take prescription nonsteroidal anti-inflammatory drugs (NSAID) with acetaminophen (Tylenol). The alternative is to take prescription low-dose opioid medications with acetaminophen. This study is being done to learn which option works the best at relieving pain and has the least amount of side effects.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Adults having one of three common surgical procedures can take part in the study if they do not have significant pain medication use before surgery. The three procedures are gallbladder removal, hernia repair, and breast lump removal.

Persons who are unable to take commonly used pain medications are not eligible. Those pain medications include Tylenol (acetaminophen), non-steroidal anti-inflammatory drugs (ibuprofen, celecoxib, naproxen), or low-dose opioid medications (oxycodone, morphine, hydromorphone). People who anticipate having more than one surgery within 6 months are also not eligible.

3.2 How many people are expected to take part in this study?

900 persons are expected to participate, <#> at <site name> and <#> at other sites around the United States and Canada.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

A — General study procedures

- We will ask you questions using surveys that can be completed on mobile devices, computers, or by telephone calls. Patients who do not have a mobile device will be provided one by the study. Provided mobile devices will have limited data that is purchased by the study team to allow for survey completion. At the end of the 6 month participation period we ask that you return the mobile device. You can either email us at <study email> or call us at <study phone> and we will send you a return envelope to return the device.
- Before surgery (up to two weeks prior), you will answer several questions in a survey that will act as a “baseline” for comparisons to questions asked later in the study.
- You will be randomized to one of two options to treat pain at home after discharge from surgery.
    - Option 1 - acetaminophen with a non-steroidal anti-inflammatory drug.
    - Option 2 - acetaminophen with a low-dose opioid.
- You will have a 50:50 chance of being assigned to each of the two options.
- Your surgical team or the research team will prescribe you one of the two options to treat pain after surgery. Receiving a prescription for medication to treat your pain after surgery is a part of your routine care.
- You will know which option you are assigned to because you will be given the prescriptions to take to the pharmacy.
- You will be asked to complete a brief survey after surgery every day for one week.
- You will be asked to complete other surveys after surgery at 1 week, 1 month, 3 months, and 6 months after surgery.
- The research team will look at your health records to understand your experience during and after surgery. These will include your surgical and medical care and prescription

medications in the electronic health record, and prescription medications in the <name of Prescription Drug Monitoring Program>.

- Results from the surveys and study measures will not be a part of your routine clinical care. Completing surveys and study measures are only part of the research study.
- After the study, you will have the option to learn about the published results from the study. These results are not individualized.

By participating in this research study, you will have certain responsibilities, like making sure that you fill out all of your scheduled surveys and reporting any adverse reactions you may have during the study. An adverse reaction is any unexpected or dangerous reaction to a medication. The adverse reaction may be sudden like anaphylaxis or develop over time like gastrointestinal bleeding. If you experience any symptoms and/or injuries during the whole duration of your participation in the study, please report these to the study team at <study email>.

B – Sub-study with specified design

<Information on substudy, if applicable to site>

C – Collection for unspecified future research

The following information is specific to unspecified future use of identifiable data and/or biospecimens. We would also like your permission to keep some of your medical information collected in the main study, so that we may study it in future research. The future research may be similar to this study or may be completely different.

You can take part in the main study even if you decide not to let us keep your medical information for future research. If you give us your permission, we will use your medical information for future research. Even if you give us permission now to keep some of your medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your medical information, we may not be able to take the information out of our research.

We may share your medical information with other researchers, so that they can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your medical information with other researchers, we will not be able to get it back. Future use of your identifiable data and/or specimens will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your medical information. Allowing us to do future research on your medical information will not benefit you directly. With appropriate permissions, your collected information may also be shared with other researchers here, around the world, and with companies. Your identifiable private information may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

4.2 How much of my time will be needed to take part in this study?

You will fill out surveys before your surgery and after you are discharged from surgery. Before surgery the surveys should take 20-30 minutes to complete. We will ask you to fill out a daily survey for the first week that is expected to take less than 5 minutes each day. After that, we will ask you to complete surveys less often - at least three times over the next 6 months. Each survey should take about 15 minutes.

4.3 When will my participation in the study be over?

Most subjects will complete their part in the study within about **6 months.** The entire study is expected to last about **3 years**.

4.4 What will happen with my information and/or biospecimens used in this study?
Your collected information may be shared with the Patient-Centered Outcomes Research Institute.

With appropriate permissions, your collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The risks to joining this study are not expected to be any greater than the risks associated with taking typical pain medications prescribed after surgery. The known or expected risks, and steps to minimize these risks, are as follows:

1. Inadequate or poor pain control after surgery:

   Background: The two options in the study are common pain-relieving medications. Both options are in routine use by patients having your surgery and are recommended by clinical guidelines. Since the two medication options being compared in the study are the most commonly used ways of treating post-surgical pain, the risk of inadequate pain control is expected to be similar to usual care.

   Steps taken by the research team to minimize this risk: The two options chosen for this study have been shown to effectively treat pain after surgery. Ensuring that your pain is treated adequately is a top priority of the study. By participating in this study, you will still be able to receive additional pain medication from your surgical team if you need it.

   If you experience poor pain control, you will be encouraged to contact your surgeon just as you would do were you not in the study. Your surgical team will learn about your pain and determine the most appropriate next step.

   After speaking with your surgical team, you may be able to take additional doses of the medication you are prescribed after surgery. If pain control continues to be a problem, your surgical team may prescribe you a different type of medication to help with your pain. You may receive additional pain treatments at their direction.

2. Discomfort from being asked personal questions on sensitive topics:

Background: This risk may result from being asked personal questions on sensitive topics. It is expected to be rare.

Steps taken by the research team to minimize this risk: Any person becoming distressed while completing questions will be encouraged to pause and ask a study team member to clarify and/or discuss the item that they find to be unclear or troubling. If needed, the person may skip any question that they find distressing.

3. Side effects from pain medication:

Background: All medications can have side effects, including those included in the study. Side effects from both types of pain medications are expected based on reports from patients who have taken these medications in the past.

Steps taken by the research team to minimize this risk: Doses for both types of pain medications are within the range that are usually given after surgery. You will be asked about any side effects in study surveys. You may stop taking the pain medications at any time that you choose. You may also contact the surgical team to discuss any significant side effects as you would if you were not in the study.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy, including a certificate that adds special protections for confidentiality to your data.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The research team has taken steps to minimize the risks of this study. Even so, you may still have problems or side effects as a part of this study, even when the study team is careful to avoid them. Telling the research team about side effects is a planned part of this study.

Please tell the researchers listed in Section 10 about any injuries or other problems that you have during this study. You should also tell your regular doctors. If you have a complication or adverse effects, the research team will communicate with your surgical team to determine the best next step. A medication dose could be lowered, stopped, or changed to a different medication.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the research team involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. However, others may benefit from the knowledge gained from this study. Findings from this study have the potential to help people undergoing surgery, their families, and their doctors make choices about how to manage pain and take the best type of pain medicine.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the research team will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined

the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?
Your surgeon would typically prescribe one of the two medication options for acute pain after surgery without participating in the study. There may be other ways of treating your pain after surgery, including using only Tylenol or using non-medication treatments.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the research team why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10.

7.2 Could there be any harm to me if I decide to leave the study before it is finished? No. Harm is not anticipated if you decide to leave the study before it is finished.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the research team may need to end your participation in the study. Some examples are:

- The research team believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the research team.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Prescription medication to treat your pain after surgery
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer. By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You are eligible to receive up to $80 for completing participation in the study. You will receive the $80 via a reloadable gift card that is sent out. You can expect the funds within 1-2 weeks of

completing the surveys for each timepoint. This includes completing the baseline survey ($15) and surveys after surgery including daily short surveys in the first week ($15 total), the 1 week survey ($10), 1 month survey ($15), 3 month survey ($10) and 6 month survey ($15). If you decide to leave the study early, you will not be paid for the surveys that you did not complete.

8.3 Who could profit or financially benefit from the study results?
No person or organization has a financial interest in the outcome of the study. Research can lead to new discoveries, such as new tests, drugs, or devices. The research team, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my information?
Research records will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the research team to link the information to you. The file is an electronic file that is stored via the cloud/shared drives. Only approved members of the research team will have access to the files.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The research team with this Certificate may not disclose or use information or documents that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use.

Information or documents protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency funding the project that is needed for auditing or program evaluation by the Patient-Centered Outcomes Research Institute which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the research team to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of harm to self or others. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

If you tell us or we learn something that makes us believe that you or others have been or may be harmed, we may be required to report that information to the appropriate agencies.

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the research team your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Alcohol/substance abuse treatment records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the research team or others during or after this study. Examples include:

- The research team may need the information to make sure you can take part in the study.
- The research team may need the information to look for side effects or check your test results.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - o Make sure the study is done safely and properly
    - o Learn more about side effects
    - o Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The research team may need to use the information to create a database of information about your condition or its treatment.
- Information about your study participation may appear in your regular <site> medical record.
- If you receive any payments for taking part in this study, the <site> finance department will need your name and address for tax reporting purposes. In a calendar year if: 1) your payments total greater than $400 for this study or 2) if you receive payments of greater than $400 for being in more than one study, the <site> finance department will also require your Social Security Number for tax reporting purposes. If you do not wish to provide your Social Security Number, you may continue to participate in research studies, but you will not be able to receive payment for the remainder of the calendar year.

- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?
As a rule, the research team will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the <site> Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the <site> "Notice of Privacy Practices". This information is also available on the web at <site URL link>. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?
Your permission will not expire unless you cancel it. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: <name>
Mailing Address: <address>
Telephone: <site phone>
Study Coordinator: <name>
Mailing Address: <address>
Telephone: <phone>

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

<site> Institutional Review Board
<address>
Telephone: <phone>
Fax: <fax>
e-mail: <email>

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the <site> Compliance Help Line at <phone>. *When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRB number (at the top of this form), and details about the problem. This will help officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.*

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular <site> medical record.)*

12. SIGNATURES

Sig-A

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with [NAME OF STUDY TEAM MEMBER OBTAINING CONSENT] _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name:

_____

Signature:

_____

Date of Signature (mm/dd/yy): _____

Sig-D

Consent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable data for use in future research. I understand that it is my choice whether or not to allow future use of my data collected for this project. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____Yes, I agree to let the study team keep my data for future research.

_____No, I do not agree to let the study team keep my data for future research.

Print Legal Name:

_____

Signature:

_____

Date of Signature (mm/dd/yy): _____