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

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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 Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) trial is a pragmatic, international, multicentre randomised trial that enrols adults undergoing three elective surgical procedures (laparoscopic cholecystectomy, breast lumpectomy, hernia repair). Participants are randomised to receive discharge analgesic prescriptions that consist of either NSAIDs or low-dose opioids (ie, 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 7 days after surgery. The primary safety outcome is the occurrence of opioid and/or NSAID side effects over the first 7 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 utilisation 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 organisations, and other multimedia communication materials.

Trial registration number NCT05722002.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) examines patient-centred 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 standardised 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 randomised 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 characterised for surgical patients.

The Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) trial evaluates multiple patient-centred 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 hypothesise that patients who receive NSAID analgesic regimens will have less acute pain over 7 days after surgery compared with patients who receive opioid analgesic regimens. Further, we hypothesise that patients who receive NSAID versus 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 hypothesise that patients who receive NSAID versus 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 randomised 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 emphasises one type of NSAID non-opioid medication taken with acetaminophen, or (2) the opioid arm, which emphasises the use of one opioid analgesic taken with acetaminophen. CARES randomises 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 are the same for both arms; only the prescribing strategy assignment differs between them. The CARES study group is described in online supplemental appendix. Multiple trade-offs between pragmatic/effectiveness and explanatory/efficacy trial designs were considered, with a full PRECIS-2 assessment to characterise these choices across nine domains (figure 1, online 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:

1. 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.
2. 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 USA) and involve diverse populations.[1]

As a pragmatic trial, this study enrols a generalisable 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: (1) schizophrenia, bipolar disorder or other psychosis; (2) anticipated other surgery within 6 months and (3) 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

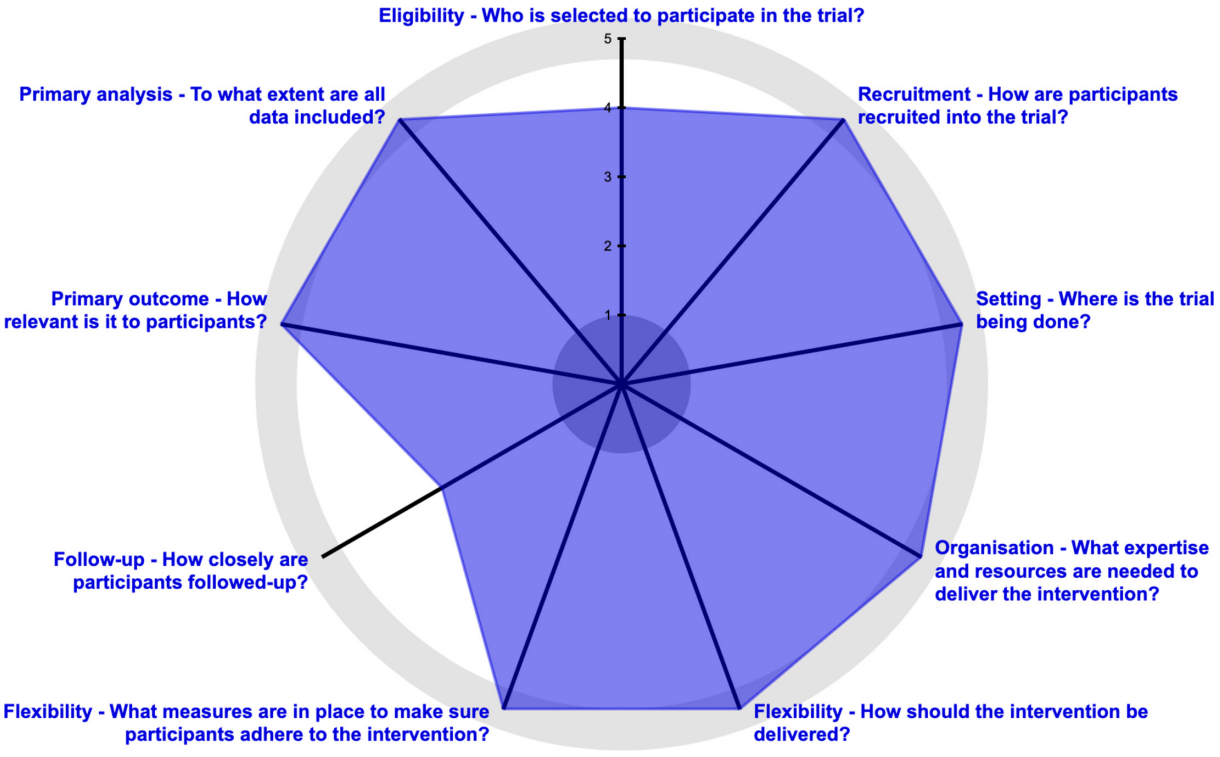

Figure 1 Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) trial PRECIS-2 wheel. Nine listed domains for the Comparing Analgesic Regimen Effectiveness and Safety after Surgery (CARES) study and the PRECIS-2 Wheel are described in relation to design aspects common to pragmatic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

disease or failure, estimated glomerular filtration rate (GFR) <60 mL/min, heart failure, peptic ulcer disease, anticoagulation, heart surgery, acute psychiatric instability (defined as current uncontrolled severe depression, severe post-traumatic stress disorder 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, anaesthesia clinics and/or local electronic health record searches for eligible patients. Searches are updated at least every month during the enrolment 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 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 (eg, 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 authorisation, the baseline survey is conducted via the mobile app. A second method of enrolment 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 enrol. Initial enrolment targets are anticipated to be balanced across sites, with flexibility to modify targets as the study progresses.

Randomisation, masking and allocation concealment

Participants provide informed consent and complete the baseline assessment before surgery. On the day of surgery, patients are randomised to the NSAID or the opioid arm. Randomisation is stratified by type of surgery (laparoscopic cholecystectomy, inguinal hernia repair, breast lumpectomy) to assure balanced numbers of participants undergoing each procedure. Randomisation 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, randomisation 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 minimise 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 randomised controlled trials.[2] Both prescribing strategies are operationalised 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 6 hours around the clock for 3 days, then as needed for pain thereafter (total #10 doses).*
- *Celecoxib 400 mg by mouth once then 200 mg every 12 hours around the clock for 3 days, then as needed for pain thereafter (total #10 doses).*
- *Naproxen 500 mg by mouth once then 250 mg every 8 hours around the clock for 3 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 4–6 hours as needed for pain (total #10 doses).*
- *Morphine 7.5 mg by mouth every 4–6 hours as needed for pain (total #10 doses).*
- *Hydromorphone 2 mg by mouth every 4–6 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 3 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 anaesthetics provided by the surgical team in the operating room.

Recommendations for the 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 (eg, bleeding) are evaluated by a study physician and reported to the patient's surgical provider. Potentially urgent adverse events (eg, 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 min at baseline, 3 months and 6 months; and approximately 15 min at 1 week and 1 month. A small, graded incentive (in increments increasing from US$10 to US$15, totalling US$80 for the 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

Table 1 Patient-reported outcome assessment schedule

Domain	Measure	Schedule					
		Baseline	Days 1–7	1 week	1 month	3 months	6 months
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		Day 3	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 utilisation				X		X

PROMIS, Patient-Reported Outcomes Measurement Information System; TAPS, Tobacco, Alcohol, Prescription medications and other Substance use.

their symptoms and perceived benefit from therapeutic disclosure.

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 randomisation, 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 min. 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 the procedures included in CARES by this time.

Table 2 Postoperative adverse medication-related symptoms for the Comparing Analgesic Regimen Effectiveness and Safety after Surgery trial

Have you experienced any of these symptoms today? Select all that apply.	
☐ Nausea	☐ Vomiting
☐ Constipation	☐ Diarrhoea
☐ Itching (pruritus)	☐ None
Have you experienced any of these symptoms today? Select all that apply.	
☐ Stomach pain	☐ Difficulty sleeping (insomnia)
☐ Heartburn	☐ Generalised 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 selects from the following options:	
☐ Mild ☐ Moderate ☐ Severe	

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 min to measure pain-related function.[8–11] A seven-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]

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 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 V.1.0 has been validated as four 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 V.2.1) 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 four-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, 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 utilisation at 1 and 6 months after surgery, including unplanned postoperative clinical interactions related to pain (patient messages, phone

Table 3 Comparing Analgesic Regimen Effectiveness and Safety after Surgery 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)	

Responses include options based on the Michigan Surgical Quality Collaborative postoperative survey, Komann *et al*, and Fan *et al*[13 14]
CBD, Cannabidiol; TENS, Transcutaneous Electrical Nerve Stimulation.

calls, non-routine clinic visits related to pain), emergency room visits and hospitalisations.

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 (Patient Health Questionnaire [PHQ]-2),[35] anxiety (Generalized Anxiety Disorder [GAD]-2),[36] the Pain Catastrophizing Scale (shortform 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 Post Anesthesia Care Unit (PACU) course. The local study team reviews a participant's chart to assess for clinically important adverse events at the end of the study

Table 4 Comparing Analgesic Regimen Effectiveness and Safety after Surgery measures on expectations prior to surgery

Statement or question	Responses
Please indicate your expectations regarding your surgery and healthcare team, using a 0–10 scale, for the following items. (*Randomise 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 1 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

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

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

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 are 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 enrolment using electronic case report forms (eCRFs). MyDataHelps includes customisable, data-driven eCRFs to capture data gathered by research coordinators at each site. Standardised 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 (eg, 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, randomised 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 (ie, BPI) and adverse effect (eg, symptom checklist) measures.

Sample size and power

The sample size for CARES was calculated based on testing the superiority of NSAID versus opiod analgesic regimens on effectiveness for acute pain. Because the surgical community has considered pain and postdischarge 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 (ie, 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 generalized estimating equations (GEE) models will be improved by the repeated outcome measures. The outcome measure for BPI pain intensity has a mean of ~3.4 (SD 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 15% for 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 eight prespecified comparisons (two 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 formalised 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 (eg, surgeon, anaesthesiologist, biostatistician with clinical trials experience, patient partner, etc) 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 enrolment 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, enrolment 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 randomised.[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 12 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 organisations.

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 3–4 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 (ie, 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-centredness, 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. Enrolment is anticipated to continue until 2026. A model consent form is provided in online supplemental exhibit 2.

CARES trial results have significant potential for reproduction, dissemination and implementation across the USA and Canada. The CARES trial proposal has been carefully designed to include characteristics that maximise 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 organisations, 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 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 organised 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 favouring 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 versus 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 randomised controlled trial that enrols 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-centred 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 postdischarge analgesic regimen that maximises pain relief while minimising adverse effects for millions of patients who undergo these procedures every year.

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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. CB reports consulting fees from Merck, Vertex, and expert witness testimony unrelated to this work.

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REFERENCES

1 Steiner CA, Karaca Z, Moore BJ, *et al*. *Surgeries in hospital-based ambulatory surgery and hospital inpatient settings*. Rockville (MD): Agency for Healthcare Research and Quality (US), 2014.
2 Moore RA, Derry S, Aldington D, *et al*. Single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2015;2015:CD008659.

3 Cooper SA, Desjardins PJ, Turk DC, *et al*. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. *Pain* 2016;157:288–301.
4 Mendoza TR, Chen C, Brugger A, *et al*. The utility and validity of the modified brief pain inventory in a multiple-dose postoperative analgesic trial. *Clin J Pain* 2004;20:357–62.
5 Smith SM, Wang AT, Katz NP, *et al*. Adverse event assessment, analysis, and reporting in recent published analgesic clinical trials: ACTTION systematic review and recommendations. *Pain* 2013;154:997–1008.
6 Weingart SN, Gandhi TK, Seger AC, *et al*. Patient-reported medication symptoms in primary care. *Arch Intern Med* 2005;165:234–40.
7 Moore RA, Derry S, Aldington D, *et al*. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2015;2015:CD011407.
8 Kim J, Chung H, Amtmann D, *et al*. Measurement invariance of the PROMIS pain interference item bank across community and clinical samples. *Qual Life Res* 2013;22:501–7.
9 Amtmann D, Cook KF, Jensen MP, *et al*. Development of a PROMIS item bank to measure pain interference. *Pain* 2010;150:173–82.
10 Cella D, Riley W, Stone A, *et al*. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol* 2010;63:1179–94.
11 Askew RL, Cook KF, Revicki DA, *et al*. Evidence from diverse clinical populations supported clinical validity of PROMIS pain interference and pain behavior. *J Clin Epidemiol* 2016;73:103–11.
12 Fischer D, Stewart AL, Bloch DA, *et al*. Capturing the patient's view of change as a clinical outcome measure. *JAMA* 1999;282:1157–62.
13 Komann M, Weinmann C, Schwenkglenks M, *et al*. Non-Pharmacological Methods and Post-Operative Pain Relief: An Observational Study. *Anesth Pain Med* 2019;9:e84674.
14 Fan M, Chen Z. A systematic review of non-pharmacological interventions used for pain relief after orthopedic surgical procedures. *Exp Ther Med* 2020;20:36.
15 Brummett CM, Bakshi RR, Goesling J, *et al*. Preliminary validation of the Michigan Body Map. *Pain* 2016;157:1205–12.
16 Hassett AL, Pierce J, Goesling J, *et al*. Initial validation of the electronic form of the Michigan Body Map. *Reg Anesth Pain Med* 2019:rapm-2019-101084.
17 Yu L, Buysse DJ, Germain A, *et al*. Development of short forms from the PROMIS™ sleep disturbance and Sleep-Related Impairment item banks. *Behav Sleep Med* 2011;10:6–24.
18 Buysse DJ, Yu L, Moul DE, *et al*. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 2010;33:781–92.
19 Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332–40.
20 Kleif J, Gögenur I. Severity classification of the quality of recovery-15 score-An observational study. *J Surg Res* 2018;225:101–7.
21 Hanmer J, Dewitt B, Yu L, *et al*. Cross-sectional validation of the PROMIS-Preference scoring system. *PLoS One* 2018;13:e0201093.
22 Wu L-T, McNeely J, Subramaniam GA, *et al*. Design of the NIDA clinical trials network validation study of tobacco, alcohol, prescription medications, and substance use/misuse (TAPS) tool. *Contemp Clin Trials* 2016;50:90–7.
23 McNeely J, Wu L-T, Subramaniam G, *et al*. Performance of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool for Substance Use Screening in Primary Care Patients. *Ann Intern Med* 2016;165:690–9.
24 Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: results from the 2019 National Survey on Drug Use and Health (HHS Publication No. PEP20-07- 01-001, NSDUH Series H-55*). Rockville, MD, 2020.
25 Hughes A, Williams M, Lipari R, *et al*. Prescription drug use and misuse in the United States: results from the 2015 National Survey on Drug Use and Health. *NSDUH Data Rev* 2016.
26 Luby AO, Alessio-Bilowus D, Hu HM, *et al*. Trends in Opioid Prescribing and New Persistent Opioid Use After Surgery in the United States. *Ann Surg* 2025;281:347–52.
27 PhenX toolkit: domains. Available: https://www.phenxtoolkit.org/protocols/view/10101 [Accessed 16 Jan 2025].
28 PhenX toolkit: protocols. Available: https://www.phenxtoolkit.org/protocols/view/10903 [Accessed 16 Jan 2025].
29 PhenX toolkit: protocols. Available: https://www.phenxtoolkit.org/protocols/view/11002 [Accessed 16 Jan 2025].
30 PhenX toolkit: protocols. Available: https://www.phenxtoolkit.org/protocols/view/11301 [Accessed 16 Jan 2025].
31 PhenX toolkit: protocols. Available: https://www.phenxtoolkit.org/protocols/view/11502 [Accessed 16 Jan 2025].
32 PhenX toolkit: protocols. Available: https://www.phenxtoolkit.org/protocols/view/11601 [Accessed 16 Jan 2025].
33 PhenX toolkit: protocols. Available: https://www.phenxtoolkit.org/protocols/view/11801 [Accessed 16 Jan 2025].
34 Sundararajan V, Quan H, Halfon P, *et al*. Cross-national comparative performance of three versions of the ICD-10 Charlson index. *Med Care* 2007;45:1210–5.
35 Kroenke K, Spitzer RL, Williams JBW. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 2003;41:1284–92.
36 Kroenke K, Spitzer RL, Williams JBW, *et al*. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007;146:317–25.
37 McWilliams LA, Kowal J, Wilson KG. Pain catastrophizing scale--short form. PsycTESTS dataset. 2017.
38 American College of Surgeons National Surgical Quality Improvement Program. *User guide for the 2019 ACS NSQIP participant use file (PUF)*. 2020.
39 Opioid prescribing. n.d. Available: https://michigan-open.org/prescribing-recommendations/
40 Overton HN, Hanna MN, Bruhn WE, *et al*. Opioid-Prescribing Guidelines for Common Surgical Procedures: An Expert Panel Consensus. *J Am Coll Surg* 2018;227:411–8.
41 National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Evidence-Based Clinical Practice Guidelines for Prescribing Opioids for Acute Pain. *Framing opioid prescribing guidelines for acute pain: developing the evidence*. Washington (DC): National Academies Press (US), 2019.
42 Hill MV, Stucke RS, Billmeier SE, *et al*. Guideline for Discharge Opioid Prescriptions after Inpatient General Surgical Procedures. *J Am Coll Surg* 2018;226:996–1003.
43 Tighe PJ, Le-Wendling LT, Patel A, *et al*. Clinically derived early postoperative pain trajectories differ by age, sex, and type of surgery. *Pain* 2015;156:609–17.
44 Olsen MF, Bjerre E, Hansen MD, *et al*. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med* 2017;15:35.
45 Myles PS, Myles DB, Galagher W, *et al*. Measuring acute postoperative pain using the visual analog scale: the minimal clinically important difference and patient acceptable symptom state. *Br J Anaesth* 2017;118:424–9.
46 Watt-Watson J, Chung F, Chan VWS, *et al*. Pain management following discharge after ambulatory same-day surgery. *J Nurs Manag* 2004;12:153–61.
47 Meghani SH, Byun E, Gallagher RM. Time to take stock: a meta-analysis and systematic review of analgesic treatment disparities for pain in the United States. *Pain Med* 2012;13:150–74.
48 Hyung B, Bicket MC, Brull R, *et al*. Prospective preference assessment for the Comparison of Analgesic Regimen Effectiveness and Safety in Surgery (CARES) trial. *Trials* 2022;23:195.
49 Overdose prevention engagement network (OPEN). n.d. Available: https://www.michigan-open.org
50 Dowell D, Ragan KR, Jones CM, *et al*. CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. *MMWR Recomm Rep* 2022;71:1–95.
51 Brown CS, Vu JV, Howard RA, *et al*. Assessment of a quality improvement intervention to decrease opioid prescribing in a regional health system. *BMJ Qual Saf* 2021;30:251–9.
52 Vu JV, Howard RA, Gunaseelan V, *et al*. Statewide Implementation of Postoperative Opioid Prescribing Guidelines. *N Engl J Med* 2019;381:680–2.
53 Kulkarni AJ, Gunaseelan V, Brummett CM, *et al*. Postoperative Opioid Consumption After Discharge: An Update From the Michigan Surgical Quality Collaborative Registry. *Ann Surg Open* 2024;5:e517.