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# Association Between Opioid Use and the Development of Diverticulitis

**Authors:** Michael Webster-Clark, Robert Platt, Greg Carney, Matt Dahl, Antonios Douros, Christopher Filliter, Amani Hamad, Tyrone Harrison, Donica Janzen, David Juurlink, Jason Kim, Xinya Lu, Carolina Moriello, J. Michael Paterson, Audray St-Jean, Laura Targownik, Fangyun Wu, Jianguo Zhang

This observational study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post-Market Drug Evaluation CoLab Network.

# Key Messages

**Opioids are commonly used for the treatment of severe pain but can cause constipation, and their link with diverticulitis** (inflammation of the small pouches in the colon) is not well understood.

**We evaluated the feasibility and then conducted a comparative safety study** to assess whether short-term and long-term opioid use is associated with an increased risk of diverticulitis in patients treated with opioids for various indications.

**In the primary comparative safety analysis, we identified 23,084,410 patients with a postsurgical indication** across 5 Canadian provinces, the UK Clinical Practice Research Datalink (CPRD), and the US Merative MarketScan databases.

**Starting opioid treatment within 7 days of surgery** and continuing use at least to the end of the follow-up period (compared to not starting opioids) **was associated with increased rates of diverticulitis** (7.97 additional events per 10,000 person-years) **and severe diverticulitis** (3.36 additional events per 10,000 person-years) **in the postsurgical indication**, although the increase was not statistically significant for the less severe outcome.

**Subgroup analyses and analyses of the trauma indication** (9.73 additional diverticulitis and 5.78 additional severe diverticulitis events per 10,000 person-years) **and other pain indications** (12.49 additional diverticulitis and 11.08 additional severe diverticulitis events per 10,000 person-years) **showed larger** relative and absolute rate increases per 10,000 person-years than analyses in the postsurgical indication cohort.

**Findings suggest health care providers may need to be particularly cautious with long-term opioid use in older patients** and watch for signs of diverticulitis, despite the overall low rates in the general population. Findings should be interpreted with the understanding of the considerable assumptions and limitations of the analysis.

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# Abbreviations

| | |
|---|---|
| **CI** | confidence interval |
| **CNODES** | Canadian Network for Observational Drug Effect Studies |
| **CPRD** | Clinical Practice Research Datalink |
| **ED** | emergency department |
| **IPCW** | inverse probability of censoring weights |
| **IPTW** | inverse probability of treatment weights |
| **IRD** | incidence rate difference |
| **IRR** | incidence rate ratio |
| **RD** | risk difference |
| **RR** | risk ratio |
| **SMD** | standardized mean difference |

# Introduction and Rationale

## Background

Opioids have long been used to treat pain. Since morphine was originally extracted from poppies and then successfully marketed by Merck at the start of the 19th century, there has been a wide array of opioid derivatives introduced including completely synthetic opioid products.[1] Opioids act on opioid receptors to dull pain, but they also slow the movement of food and increase water absorption within the gastrointestinal tract. This can lead to constipation, even during a relatively short course of opioid treatment.[2,3] Treating opioid-induced constipation while maintaining the patient on opioids to relieve pain can be extremely difficult. Whether constipation occurs due to opioid use or because of other factors, protracted constipation can lead to a diverse array of complications. These can include severe pain, hemorrhoids, and longer-term damage like impaction or anal fissures.[3]

One important unanswered question is whether opioids, presumably through opioid-induced constipation, increase the risk of diverticulitis, an illness caused by inflammation and/or infection of small sacs within the large intestine called diverticula.[4-9] While many cases of diverticulitis are mild and can be treated with antibiotics at home, it can also be life-threatening. There is a biologically plausible mechanism to explain this whereby opioids induce constipation, leading to increased pressure in the colon and more diverticula, and the increased length of exposure of these diverticula to bowel contents increases the risk of diverticulitis.[3] Randomized controlled trials of opioid therapies have been too small to show an increase in the rate of this rare outcome, especially among younger adults, who are at low baseline risk of diverticulitis. As a result, the majority of the evidence on any association between opioids and diverticulitis has come from observational studies.[5-9] In addition to being limited by potential confounding bias, these studies also have to contend with the fact that the primary symptom of diverticulitis is severe abdominal pain, which in turn is often treated with opioids. If not accounted for, this can result in protopathic bias that spuriously increases the observed risk of diverticulitis in opioid users relative to nonusers. By identifying new users of opioids following a clearly recorded indication for opioid treatment (e.g., surgery, trauma, dental procedure, or other defined indications) and comparing them to noninitiators following the same indication, we could mitigate the chance of observing such protopathic bias. Additional comparisons between new users and prevalent users following the indication could help identify differences in underlying risk between the 2 populations and help avoid the biases associated with prevalent users that are frequently observed in studies that combine new users and prevalent users into 1 exposure category.

**Main Take-Aways**

Opioids are commonly used for the treatment of severe pain but can cause constipation, and their link with diverticulitis (inflammation of the small pouches in the colon) is not well understood.

### Policy Issue

Opioid use is a potential risk factor for diverticulitis; however, evidence on the association between opioid analgesics and diverticulitis is limited. Health Canada will use the findings to better understand this risk and determine whether regulatory actions are required.

### Policy Questions

1. Are adult patients who are exposed to opioids more likely to develop diverticulitis?
2. Is there a specific group of patients (emphasis on Sex- and Gender-Based Analysis Plus [SGBA Plus]) more at risk?
3. Does the risk of diverticulitis change according to the indication for opioid use?

**Main Take-Aways**

Evidence on the association between the use of opioids and the risk of diverticulitis is limited. The overall objective of this study was to evaluate the feasibility of, and then conduct a comparative safety study to evaluate whether short-term and long-term opioid use is associated with an increased risk of diverticulitis in patients treated with opioids for different indications.

## Research Questions

1. What is the risk of diverticulitis in adult patients after exposure to opioids?
2. Does the risk of diverticulitis vary by age, sex, and indication?

## Objectives

The overall aim of this study was to evaluate the feasibility of, and subsequently conduct, an observational study evaluating whether short-term and sustained opioid use are associated with elevated risks of diverticulitis in patients with an indication for treatment with opioids.

The query was conducted in 2 parts: a feasibility study and a comparative safety study.

### Feasibility Study Objectives

1. To describe the patient characteristics and prevalence of new users, prevalent users, and nonusers of opioids within a variety of indications for opioid therapy.
2. To evaluate the incidence rates of diverticulitis according to 5 different administrative health data case definitions selected to represent increasing severity of diverticulitis within each of these indication-specific cohorts.

**Comparative Safety Study Objectives**

1. To describe patient characteristics and prevalence of new users, prevalent users, and nonusers of opioids within the 90 days preceding and 7 days (for postsurgical pain) and 30 days (for trauma or other pain indications) following the inciting event, hereafter referred to as the landmark period.
2. To compare estimates of the incidence rate ratio (IRR), incidence rate difference (IRD), and risk ratio (RR) and risk difference (RD) at 30 and 730 days for diverticulitis and severe diverticulitis comparing new users of opioids, prevalent users of opioids, and nonusers of opioids before and after adjusting for confounding variables.

# Methods

## Population and Setting

This study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES).[10,11] The study protocol was registered on the Heads of Medicines Agencies-European Medicines Agency catalogue of real-world data studies (study ID: 104165). The study population consisted of individuals who had an indication for opioid use (subsequently described) between April 1, 2004, and March 31, 2020, in 5 Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan), the UK, and the US. We selected 2004 as the beginning of the study period as this marks the introduction of the International Classification of Diseases, 10th Revision with Canadian enhancement and Canadian Classification of Health Interventions coding schemes in Canada. We selected March 2020 as the end of the study period as this marks the beginning of the COVID-19 pandemic, during which access to many health services was limited for an extended period.

## Study Design

### Feasibility Study

This multicentre retrospective descriptive cohort study explored the feasibility of a landmark-style comparative study contrasting new users of opioids, prevalent users of opioids, and nonusers of opioids following surgery, pain after trauma, dental pain, and other indications for opioid use. A landmark-style comparative study considers exposures in the time window between a signal index event creating a potential indication for opioid use (e.g., surgery leading to postsurgical pain) and a set landmark time (typically a set time postindex event) as exposed. The number of individuals within each exposure group and outcome rates for a wide spectrum of outcome definitions were determined. We also explored how varying study parameters such as landmark date, lookback period, and type of as-treated follow-up might influence the size and composition of the study cohorts and variation in these impacts across the different sites.

**Note:** British Columbia and the UK CPRD encountered data access delays and therefore the comparative safety study analyses were prioritized and the results from the feasibility study in other sites (with some additional analyses examining potential landmark windows in the UK CPRD data due to its potential

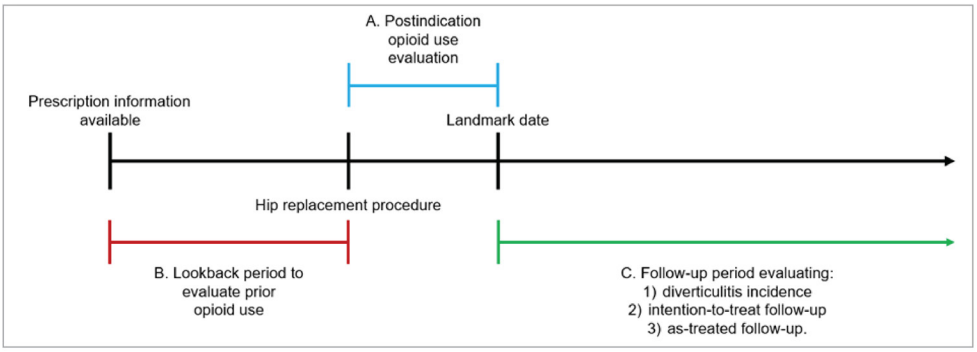
heterogeneity as a general practitioner medical record, rather than claims data) were deemed sufficient to establish feasibility.

### Comparative Safety Study

The comparative safety study was a multicentre retrospective cohort study comparing new users of opioids, prevalent users of opioids, and nonusers following defined indications for opioid therapy including postsurgical pain, trauma, and select other indications. While we were interested in estimating effects for all 3 indications to examine potential heterogeneity in absolute and relative-scale effect estimates, we prioritized the results of the postsurgical analysis because it involved the best-defined indications for opioid use with the least potential for protopathic bias. The study design diagram for the comparative safety study is depicted in Figure 1.

**Note:** All sites contributed to the postsurgical pain indication cohort. Due to time and data constraints, British Columbia was unable to contribute to the other pain cohort, and the UK CPRD and US Merative MarketScan only contributed to the postsurgical pain cohort.

## Figure 1: Study Design Diagram




## Eligibility Criteria

For the feasibility study, separate study cohorts for each of the 4 potential study indications: postsurgical pain, pain after trauma, dental pain, and other indications for opioids with specific encounter dates were constructed. The criteria for these indications were adapted from the stepwise approach employed by Pasricha et al.[12] and were identified using inpatient and outpatient health care encounter procedure and diagnosis codes. Each indication cohort included several subclasses. For example, the postsurgical indication cohort included common excisions, hip and knee replacements, hernia repairs, Caesarean sections, and a mix of other less frequent elective surgical procedures. Note that the other surgery subclass was not included in the CPRD for the postsurgical indication cohort due to CPRD limitations regarding the size of data extractions. The list of codes for the subclasses is provided in Appendix 1, Table 10.

Individuals aged 18 years and older were eligible for inclusion as of their date of eligibility for health care coverage in their administrative database and entered the study cohort on the date they first met the criteria for entry into each indication cohort. For cohorts defined by inpatient diagnosis or procedure codes, the

cohort entry date was the date of hospital discharge. For outpatient surgical procedures, cohort entry was the date of the procedure. Patients were not permitted to enter the cohort multiple times for a given indication but could enter multiple indication cohorts during the accrual period provided they met the criteria for cohort entry.

For the comparative safety study, individuals who met the entry criteria for multiple subclasses within an indication cohort on the same date were randomly assigned to a subclass except for in the US Merative MarketScan (they were entered in both). This occurred in a low number of patients (approximately 3% of new users and approximately 1% of nonusers were duplicate observations), meaning randomly assigning them would only slightly shift the target and comparator population's covariate distributions. Ultimately, based on the results of the feasibility analysis in Ontario, the final indications for the comparative safety study were postsurgical pain, pain after trauma, and other indications for opioid use combined (excluding dental pain). We decided to exclude dental pain rather than combine it with the other indication category because the numbers for the dental pain indication were very small, and the other indications were based on more longer-term chronic indications than treatment with opioids following a shorter-term indication such as a dental procedure.

## Data Sources

We used administrative health databases from 5 Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan), the UK CPRD (Aurum), and the US Merative MarketScan. Table 1 summarizes the contributions from each site for the feasibility and comparative safety study. Briefly, the databases contain health insurance registries, prescription drug claims, medical service claims, hospitalization records, and emergency department (ED) records (where available). The start of data availability was January 1, 2008, in Alberta. In Ontario, patient accrual began July 1, 2013, to allow a 1-year lookback period before the launch of the province's Narcotics Monitoring System, which captures all prescription opioid dispensations regardless of payer. In other study provinces these were captured in the provincial prescription drug claim databases. In the US Merative MarketScan, the start of data availability was January 1, 2006. The UK CPRD Aurum is a primary care database which contains the records of 40 million individuals (including 14 million individuals currently registered) from 1,370 general practices in the UK.[13] The UK CPRD database was linked to the Hospital Episode Statistics database, which contains hospital admission information and is available for approximately 90% of the participating practices in CPRD. UK CPRD data were also linked to national death registrations from the Office of National Statistics; this linkage is available for general practices in England who have consented to the linkage. The US Merative MarketScan database includes more than 70 million individuals covered by large employer health insurance plans in the US, and government and public organizations. The list of databases and dates of data availability in each site are reported in Appendix 1, Tables 11 and 12.

## Table 1: Contributions of Each Site to the Feasibility and Comparative Safety Study

| Follow-up and outcome type | Alberta | British Columbia | Manitoba | Ontario | Saskatchewan | US Merative MarketScan | UK CPRD |
|---|---|---|---|---|---|---|---|
| **Feasibility** | Yes | **No** | Yes | Yes | Yes | Yes | **No** |
| **Comparative safety analyses per indication** | | | | | | | |
| Postsurgical | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Trauma | Yes | Yes | Yes | Yes | Yes | **No** | **No** |
| Other pain | Yes | **No** | Yes | Yes | Yes | **No** | **No** |
| **Comparative safety analyses type and outcome for the postsurgical indication cohort** | | | | | | | |
| **As treated** | | | | | | | |
| Outcome 1 | Yes | **No** | Yes | Yes | Yes | **No** | Yes |
| Outcome 2 | **No** | Yes | Yes | Yes | **No** | Yes | Yes |
| **Intention to treat** | | | | | | | |
| Outcome 1 | Yes | **No** | Yes | Yes | Yes | **No** | Yes |
| Outcome 2 | Yes | Yes | Yes | Yes | **No** | Yes | Yes |

CPRD = Clinical Practice Research Datalink; ED = emergency department.

Notes: British Columbia and the UK CPRD were not included in the feasibility study due to data access delays. All sites contributed to the postsurgical pain indication cohort. Due to time and data constraints, British Columbia was unable to contribute to the other pain cohort, and the UK CPRD and US Merative MarketScan only contributed to the postsurgical cohort.

Outcome 1 is ED or inpatient visit for diverticulitis, and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan. British Columbia and US Merative MarketScan data were not available for outcome 1; Manitoba data were not available for ED visits for outcome 1; and Saskatchewan data were not available for outcome 2.

## Key Study Measures

### Exposures

After meeting the criteria for a given indication, patients were followed until their designated landmark date to determine whether they were dispensed (or prescribed for CPRD) an opioid. A detailed list of the study medications is included in Appendix 1, Table 13. Multiple landmark dates were evaluated in the feasibility study (7, 14, and 30 days). Because the feasibility analysis in Ontario data suggested minimal opioid initiation between 7 days and 30 days following the surgery date, we selected a 7-day landmark period for the postsurgical cohort to ensure proximity to the indication. A 30-day landmark was used for CPRD as we observed higher rates of opioid initiation between 7 days and 30 days in CPRD compared to the North American data sources, likely due to the database using physician orders rather than prescription fills; as a result, the new user population may not represent the same types of patients. We selected the 30-day landmark for the trauma and other pain indication cohorts due to more patients initiating within the 7- to 30-day window in the feasibility analyses.

Patients were then subclassified as opioid nonusers, new opioid users, and prevalent opioid users. Those with no opioid prescription records by the landmark date were classified as nonusers. Those with opioid prescription records (insurance claims in North American databases or prescription orders in the UK CPRD) by the landmark date were classified as new or prevalent users depending on their previous opioid exposure

history. New users of opioids were defined as those without any opioid prescription records within a 90-day lookback before their indication. Those with at least 1 opioid prescription record within that lookback were defined as prevalent users of opioids. We separated new users from prevalent users of opioids to avoid healthy adherer and biases associated with prevalent users (which could bias short-term results toward the null if the risk is higher in the early stages of opioid use) and ensure better alignment of the start of the hypothetical intervention and the start of follow-up.[14] Multiple lookback periods were assessed in the feasibility study (90, 180, and 365 days). A 90-day lookback was used for all indication cohorts (postsurgical, trauma, and other pain) as extending the lookback period to 365 days in the feasibility analyses did not greatly alter the distribution of prevalent and new users. In the comparative safety study, all patients were required to have at least 1 year of continuous health coverage before the cohort entry date, and those who died or otherwise left the cohort before the landmark date were excluded from the analysis. Gaps of 30 days or fewer were considered as continuous health care coverage whether before and after the landmark date.

Exposure was defined using both an intention-to-treat approach and an as-treated approach. In the intention-to-treat approach, patients were followed from the landmark date (day 7 or 30, as appropriate) until occurrence of death, end of health insurance coverage (or leaving the general practice in the CPRD), end of data availability, or end of the study period (March 31, 2020), whichever occurred first, irrespective of whether they changed their initial exposure status. In the as-treated approach, new users and prevalent users were considered continuous users until the preceding events or they discontinued opioid therapy, defined as a gap of 30 days or longer beyond the end of the days supplied in their last continuous prescription. No censoring was applied for patients switching between different types or dosages of opioids. Nonusers were followed similarly to the intention-to-treat follow-up but were censored upon initiation of opioid therapy.

### Outcomes of Interest

The outcome of interest was diverticulitis. Follow-up for the outcome began after the 7- or 30-day landmark date, as appropriate for the indication. The feasibility study explored 5 outcome definitions for diverticulitis:

1. an ED or inpatient primary discharge diagnosis for diverticulitis
2. an ED diagnosis for diverticulitis accompanied by a scan (CT or MRI) within the same ED visit
3. an inpatient primary discharge diagnosis for diverticulitis accompanied by a scan (CT or MRI) within the same hospitalization (referred hereafter as inpatient visit with a scan)
4. an inpatient visit with a scan and subsequent surgery during hospitalization
5. an inpatient visit with a scan and subsequent mortality.

Ultimately, 2 outcome definitions of differing severity were chosen for the comparative safety study: an ED or inpatient primary discharge diagnosis of diverticulitis (the first outcome from the feasibility analysis, referred hereafter as outcome 1) and more severe diverticulitis defined as an inpatient visit with a scan (the third outcome from the feasibility analysis, referred hereafter as outcome 2). The list of diagnosis and procedure codes is included in Appendix 1, Table 14. These outcome definitions were selected based on the

feasibility analysis which showed the more severe diverticulitis case definitions (i.e., those including surgery or mortality) to have too few events to be feasible. The less severe diverticulitis outcome of a diverticulitis coded as an ED visit with a CT scan was considered but ultimately dropped due to inconsistent access to physician billing data for CT scans and/or ED records across the study sites. This means that the sensitivity and specificity of outcome 1 have not been formally validated and it picks up an unknown number of cases that are not truly diverticulitis events. Due to the requirement for a CT scan, outcome 2 will be more specific, but it may also be less sensitive and omit cases of diverticulitis that can be treated at home.

For the diverticulitis outcomes involving hospitalization, the outcome event date was defined as the date of hospital admission. Risk of diverticulitis was assessed at 30, 180, and 730 days after the appropriate landmark date for the opioid indication (i.e., 7 or 30 days). When estimating incidence rates, patients were permitted to experience multiple outcome events provided they were separated by at least 30 days (meaning the ED visit or admission date for the inpatient encounter defining a subsequent outcome had to occur at least 30 days after the ED visit or inpatient encounter discharge date defining the previous outcome).

Note: Saskatchewan results were limited to outcome 1 due to unavailability of billing information for CT scans. Manitoba results were limited to hospitalization admissions for outcome 1 due to the absence of ED records. British Columbia and US Merative MarketScan results were limited to outcome 2 due to time and data constraints (Table 1).

### Covariates of Interest

Patient characteristics were assessed as of the date of cohort entry. The covariates included sociodemographic characteristics, including age, sex at birth, and socioeconomic status (using site-specific definitions). While it is unclear what variables might act as confounders, based on feedback from clinical experts we incorporated several gastrointestinal risk factors for diverticulitis, including history of irritable bowel syndrome, Crohn disease, diverticulitis, and diverticulosis, as well as the following elements of the Deyo-Charlson Comorbidity Index:[15,16] myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, transient ischemic attack, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, and current tumour (excluding nonmelanoma skin cancer). Comorbidities were assessed in the year before cohort entry using both outpatient and inpatient diagnosis codes in all Canadian provinces and the US Merative MarketScan as is conventional for insurance claims data, whereas in the UK CPRD these were assessed as ever before (i.e., using all available data before cohort entry date with a minimum of 1-year lookback) as is the convention for analyzing the general practitioner data due to the generally longer follow-up periods and, in the absence of studies attempting to examine temporal trends, a more sensitive approach to capturing potential confounding variables than shorter lookback durations.[17] While the 1-year lookback period may sometimes miss historical cases of some covariates, it was selected to avoid issues of unequal lookback between patients in US commercial claims and public insurance in Canada and enhance comparability of covariates across those data sources. While the exact meaning of the covariates differs, the total impact on confounding control and the target population from these different approaches is generally not that large. Additional covariates that are not routinely available in administrative health data were

included in the UK CPRD, which contains electronic health records data: race, ethnicity, smoking status, and body mass index.

## Analyses

### Control for Confounding

Patients who initiate opioids (or are prevalent users of opioids) after experiencing a compelling indication may differ systematically from those who do not take any opioids after the same indication, resulting in potential confounding bias. To address this bias in the comparative safety analyses, **odds weights** (also referred to as standardized morbidity ratio weights) were used to estimate the **effect specifically in opioid new users**, or the average treatment effect in the treated.[18]

We first estimated a propensity score using multivariable logistic regression based on baseline covariates (previously mentioned) and then used the estimated propensity score to calculate the odds weights. The estimation of this propensity score was stratified by indication subclass. New users were assigned a weight of 1. The weights for nonusers were determined by combining the nonuser cohort with the opioid new user cohort and then estimating conditional probabilities of being in the opioid new user group. Nonusers received weights equal to their conditional odds of being in the opioid new user group, or the probability divided by 1 minus the probability. This was then repeated with the prevalent users replacing the nonusers to calculate their weights. This analysis was performed specifically to evaluate potential biases associated with prevalent users and unmeasured confounding if new and prevalent users were treated as 1 exposure group. Standardized mean differences (SMDs) were calculated comparing new users with nonusers and with prevalent users, and weights were recreated if these differences exceeded 0.100.

To explore whether treatment effects would differ with a target population of **all individuals with the indication** (rather than new users of opioids following the indication) **inverse probability of treatment weights (IPTW)** were created for each indication subclass and exposure group to estimate effects in the overall population, or the average treatment effect.[19] Logistic regression was applied to estimate propensity scores for each exposure group conditional on the baseline covariates (previously mentioned) and then used to calculate the IPTW. For each exposure group, individuals were assigned a weight corresponding to the probability of the treatment they received divided by the conditional probability of the treatment they received. For example, new users were assigned a weight corresponding to being a new user divided by the probability of being a new user, or 1 divided by the probability. This was then repeated with the prevalent users and then nonusers. SMDs were calculated and weights were recreated if these differences exceeded 0.100.

If there were persistent issues with the SMDs exceeding 0.100 after modifying the terms in the propensity score, the weights were truncated (meaning weights with stabilized value greater than 10 were set to a value of 10) to reduce the influence of large weights on treatment effect estimates and avoid large weights resulting in poor covariate balance.

## Control for Selection Bias

Intention-to-treat and as-treated analyses were both conducted. While the administrative censoring in the intention-to-treat analysis is unlikely to generate meaningful selection bias, censoring nonusers who initiate and users who discontinue treatment in the as-treated analysis is much more likely to cause bias. To help evaluate the potential for (and address) this selection bias, inverse probability of censoring weights (IPCW) were created based on baseline covariates for the as-treated analyses.[20] To create these IPCW, a Cox proportional hazards model was fitted to predict the hazard ratio for censoring (meaning a gap in 30 days of days supply for opioid users and receipt of an opioid prescription for opioid nonusers) based on key predictors of sustained opioid use measured at baseline including age, sex, prior diverticulitis, and economic deprivation factors (where available). The coefficients from this Cox regression model were used to generate a covariate-conditional probability of remaining uncensored for each individual. Patients then received an IPCW equal to the inverse of this value. This IPCW could then be combined with odds or IPTW weights to simultaneously control for both confounding and selection bias.

## Descriptive Analysis

Descriptive statistics were used to summarize patient characteristics in each indication cohort overall in the feasibility analysis and before and after weighting in the comparative safety analysis. Continuous variables were described as mean (standard deviation) and categorical variables as frequencies and percentages. Baseline characteristics were weighted using odds and ITPW weights in separate analyses. In addition, these were combined with IPCW in the as-treated analyses. Covariate balance between the exposure groups was assessed using SMDs, with an absolute value of less than 0.100 considered good balance.[21] Crude and weighted incidence rates of diverticulitis (per 10,000 person-years) and corresponding 95% confidence intervals (CIs) were estimated within each exposure group. In the comparative safety study, the risk of diverticulitis at 30, 180, and 730 days was estimated (with a focus on risks at 30 and 730 days to capture short-term and long-term risks), while the feasibility study included additional risk estimates at 90 and 365 days. Risks were generated from the survival functions generated by the life table approach of the PHREG procedure in SAS.

## Comparative Analyses

Within each indication cohort, we estimated IRRs and IRDs, as well as 30-, 180-, and 730-day RRs and RDs comparing opioid new users to opioid nonusers and prevalent opioid users to opioid new users, respectively. Crude and weighted values were estimated. The corresponding 95% CIs for these comparative measures were estimated using 1,000 bootstrap replicates, with the lower and upper confidence limits taken from the 2.5 and 97.5 percentiles, respectively, of the bootstrap estimates, with missing results omitted from the calculation of the percentiles. The new users were determined to be significantly different from the nonusers if these 95% confidence limits did not include 1 (for the IRR and RR) or 0 (for the IRD and RD), and similarly for the prevalent users and new users.

For each indication cohort, we conducted the 3 following subgroup analyses using the as-treated follow-up: by indication subclass, by age at initial event (18 to 39 years, 40 to 64 years, and 65 years and older), and by sex. The analyses by age subgroup were repeated using the intention-to-treat follow-up. We conducted

a prespecified sensitivity analysis excluding new users and prevalent users who received opioids used in opioid maintenance therapy. These included buprenorphine, buprenorphine-naloxone combinations, and methadone. We also conducted 2 post hoc sensitivity analyses decided on during the analytic phase. First, we conducted an as-treated analysis in which odds weights and IPCW were reestimated within each bootstrap replicate (rather than using the original weights). Second, we used an intention-to-treat analysis in which individuals who did not have an opioid prescription between the index and landmark dates but did have an opioid prescription during the lookback period before the index date were excluded from the nonuser exposure group.

### Meta-Analysis

For the feasibility study, the site-specific results were pooled to understand the size and characteristics of the overall sample. We also summed the person-years and event counts to calculate a pooled incidence rate for each outcome and calculated pooled risks based on the weighted average across the sites. For the comparative safety study, site-specific IRR, IRD, RR, and RD for the severe diverticulitis outcome were pooled for each indication cohort (and, where appropriate, each potential subgroup) using DerSimonian and Laird random-effects meta-analysis.[22] The standard error of each comparative measure at each site was obtained by taking the width of the CI (for difference comparisons) or the width of the log CI (for ratio comparisons) and dividing by 3.92. Between-site heterogeneity was assessed using the $I^2$ statistic.

## Results

**Main Take-Aways From the Comparative Safety Analysis**

- We identified a total of 23,084,410 adult patients with a postsurgical indication across 5 Canadian provinces, the UK CPRD, and the US Merative MarketScan databases.
- Starting opioid treatment within 7 days of surgery and continuing use at least to the end of the follow-up period was associated with an increased rate of severe diverticulitis (3.36 additional events per 10,000 person-years) compared to not starting opioids. A small but not statistically significant increase was observed in the rate of diverticulitis (7.97 additional events per 10,000 person-years).
- In the trauma and other pain indications, larger effects were observed (5.78 and 11.08 additional severe diverticulitis events per 10,000 person-years, respectively), suggesting potentially stronger associations in some populations.

### Feasibility Study Results

#### Baseline Characteristics

Table 2 shows the total number of patients identified in each indication cohort in the feasibility analysis from Alberta, Manitoba, Ontario, Saskatchewan, and the US Merative MarketScan: 32,878,228 for the postsurgical indication; 47,187,172 for the trauma indication; 272,969 for the dental pain indication; and

56,575,733 for other pain indications. Calendar time trends in the overall cohort were generally similar across the indications. However, age varied with the dental indication being the youngest (49.8% aged 18 to 39 years), followed by other pain indication (40.5%), trauma indication (37.5%), and postsurgical indication (29.6%). In the sites with data available on socioeconomic status (all sites except the US Merative MarketScan), the distribution of individuals across quintiles was roughly equal with the exception of the dental indication, which had more individuals in the lower quintiles (25.7% in the first quintile and 20.6% in the second quintile). The comorbidities were indicative of a healthy cohort of individuals, with the exception of a proportion of tumour of 3.5% to 6.1%. Proportions of various comorbidities and risk factors varied across both indication classes and sites. Full covariate distributions for each indication by site are listed in Appendix 2, Tables 15 to 18.

## Table 2: Baseline Characteristics by Indication for the Feasibility Study

| Characteristic | Postsurgical N (%) N = 32,878,228 | Trauma N (%) N = 47,187,172 | Dental pain N (%) N = 272,969 | Other pain N (%) N = 56,575,733 |
|---|---|---|---|---|
| Nonusers | 24,869,997 (75.6) | 39,876,344 (84.5) | 155,272 (56.9) | 49,415,999 (87.3) |
| New users | 5,989,535 (18.2) | 5,154,627 (10.9) | 85,229 (31.2) | 4,855,920 (8.6) |
| Prevalent users | 2,018,696 (6.1) | 2,156,201 (4.6) | 32,468 (11.9) | 2,303,814 (4.1) |
| **Calendar year of study cohort entry[a]** | | | | |
| 2004 to 2007 | 4,573,706 (13.9) | 5,577,888 (11.8) | 35,915 (13.2) | 7,235,034 (12.8) |
| 2008 to 2011 | 11,789,924 (35.9) | 15,713,563 (33.3) | 82,315 (30.2) | 20,303,218 (35.9) |
| 2012 to 2015 | 9,219,096 (28.0) | 13,501,764 (28.6) | 75,824 (27.8) | 16,356,199 (28.9) |
| 2016 to 2020 | 7,295,502 (22.2) | 12,393,957 (26.3) | 78,915 (28.9) | 12,681,282 (22.4) |
| **Site** | | | | |
| Alberta | 660,829 (2.0) | 2,537,751 (5.4) | 6,106 (2.2) | 2,890,117 (5.1) |
| Manitoba | 438,191 (1.3) | 706,491 (1.5) | 9,262 (3.4) | 642,762 (1.1) |
| Ontario | 1,584,328 (4.8) | 1,927,461 (4.1) | 52,010 (19.1) | 1,816,978 (3.2) |
| Saskatchewan | 501,812 (1.5) | 681,017 (1.4) | 4,998 (1.8) | 627,082 (1.1) |
| US Merative MarketScan | 29,693,068 (90.3) | 41,334,452 (87.6) | 200,593 (73.5) | 50,598,794 (89.4) |
| **Age (years)** | | | | |
| 18 to 39 | 9,728,823 (29.6) | 17,691,417 (37.5) | 135,911 (49.8) | 22,926,112 (40.5) |
| 40 to 64 | 17,939,247 (54.6) | 24,008,847 (50.9) | 108,697 (39.8) | 27,511,045 (48.6) |
| 65 to 79 | 3,922,753 (11.9) | 3,787,368 (8.0) | *20,185 (7.4) | 4,229,758 (7.5) |
| 80+ | 1,287,405 (3.9) | 1,699,540 (3.6) | 8,176 (3.0) | 1,908,818 (3.4) |
| **Sex** | | | | |
| Males | 12,267,220 (37.3) | 21,630,546 (45.8) | 135,671 (49.7) | 21,975,276 (38.8) |
| Females | 20,611,008 (62.7) | 25,556,626 (54.2) | 137,298 (50.3) | 34,600,457 (61.2) |

| Characteristic | Postsurgical N (%) N = 32,878,228 | Trauma N (%) N = 47,187,172 | Dental pain N (%) N = 272,969 | Other pain N (%) N = 56,575,733 |
|---|---|---|---|---|
| **Income quintile[b]** | | | | |
| First (lowest) | 589,304 (18.5) | 1,258,899 (21.5) | 18,613 (25.7) | 1,278,713 (21.4) |
| Second | 599,180 (18.8) | 1,197,495 (20.5) | 14,914 (20.6) | 1,197,250 (20.0) |
| Third | 588,263 (18.5) | 1,111,103 (19.0) | 12,820 (17.7) | 1,100,540 (18.4) |
| Fourth | 568,490 (17.8) | 1,042,293 (17.8) | 11,230 (15.5) | 1,024,833 (17.1) |
| Fifth (highest) | 557,817 (17.5) | 1,026,325 (17.5) | 10,639 (14.7) | 999,973 (16.7) |
| **Comorbidities** | | | | |
| History of irritable bowel syndrome | 330,444 (1.0) | 444,082 (0.9) | 3,525 (1.3) | 479,454 (0.8) |
| History of Crohn disease | 118,017 (0.4) | 147,097 (0.3) | 1,096 (0.4) | 165,023 (0.3) |
| History of diverticulitis or diverticulosis | 384,311 (1.2) | 423,480 (0.9) | 2,270 (0.8) | 404,858 (0.7) |
| History of myocardial infarction | 355,020 (1.1) | 180,034 (0.4) | 5,238 (1.9) | 234,953 (0.4) |
| History of congestive heart failure | 355,796 (1.1) | 593,257 (1.3) | 6,033 (2.2) | 674,828 (1.2) |
| Peripheral vascular disease | 306,294 (0.9) | 538,465 (1.1) | 3,412 (1.2) | 579,643 (1.0) |
| Cerebrovascular accident | 494,358 (1.5) | 869,297 (1.8) | 6,815 (2.5) | 918,700 (1.6) |
| Transient ischemic attack | 91,866 (0.3) | 198,314 (0.4) | 1,070 (0.4) | 211,412 (0.4) |
| Dementia | 86,850 (0.3) | 202,221 (0.4) | 4,266 (1.6) | 175,628 (0.3) |
| Chronic obstructive pulmonary disease | 1,123,508 (3.4) | 1,670,370 (3.5) | 13,233 (4.8) | 1,891,795 (3.3) |
| Peptic ulcer disease | 129,752 (0.4) | 173,697 (0.4) | 1,454 (0.5) | 192,032 (0.3) |
| Liver disease | 246,359 (0.7) | 299,965 (0.6) | 2,495 (0.9) | 350,355 (0.6) |
| Diabetes mellitus | 3,238,787 (9.9) | 3,965,166 (8.4) | 27,133 (9.9) | 4,453,436 (7.9) |
| Hemiplegia | 17,433 (0.1) | 43,240 (0.1) | 598 (0.2) | 42,875 (0.1) |
| Chronic kidney disease | 421,493 (1.3) | 690,671 (1.5) | 5,358 (2.0) | 718,304 (1.3) |
| Current tumour | 1,889,649 (5.7) | 1,732,546 (3.7) | 16,715 (6.1) | 1,960,857 (3.5) |
| **Subclass of indication[c]** | | | | |
| Common excision | 5,892,086 (17.9) | — | — | — |
| Knee, hip, or shoulder surgery | 833,536 (2.5) | — | — | — |
| Hernia repair | 281,965 (0.9) | — | — | — |
| Caesarean section | 1,898,794 (5.8) | — | — | — |
| Other surgery | 24,453,370 (74.4) | — | — | — |
| Dislocations, sprains, and strains | — | 19,048,322 (40.4) | — | — |
| Fracture and major trauma | — | 2,367,680 (5.0) | — | — |
| Burns and wounds | — | 16,975,306 (36.0) | — | — |
| Other trauma | — | 9,493,262 (20.1) | — | — |

| Characteristic | Postsurgical N (%) N = 32,878,228 | Trauma N (%) N = 47,187,172 | Dental pain N (%) N = 272,969 | Other pain N (%) N = 56,575,733 |
|---|---|---|---|---|
| Nephrolithiasis or cholecystitis | — | — | — | 1,891,658 (3.3) |
| Headache and migraine | — | — | — | 42,967,949 (75.9) |
| Nonsurgical deliveries | — | — | — | 4,430,078 (7.8) |
| Back pain | — | — | — | 7,753,953 (13.7) |

Note: Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

[a]Alberta data were available as of 2008, Ontario as of 2013, and the US Merative MarketScan as of 2006.

[b]Site-specific definition; data were not available in the US Merative MarketScan. Missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

[c]Patients could be included in more than 1 subclass within a particular indication cohort.

## Exposure Groups

In each site participating in the feasibility analyses, there was minimal change in the proportion of individuals in the postsurgical or dental indications classified as new or prevalent users when increasing the landmark period from 7 days to 14 or 30 days. For trauma and other pain indications; however, there was a larger relative increase (e.g., 7% new users for the other pain indication at a 7-day landmark in the US Merative MarketScan versus 9% new users with a 30-day landmark). Increasing the lookback period from 90 days to 180 or 365 days resulted in some new users being classified as prevalent users across the various sites, with the shifts being smallest in the trauma indication. Table 2 also includes the number of patients included in each exposure group when using the landmark windows (7 days postsurgical and dental, 30 days trauma and other pain) and lookback periods (90 days for all indications) implemented in the comparative safety analyses. The number of potential new users was highest in the dental indication (31.2%), followed by the postsurgical (18.2%), trauma (10.9%), and other pain indications (8.6%).

The proportion of new users for the dental indication varied widely across the US Merative MarketScan (26.6%) and the provincial data (Alberta: 5.5%, Manitoba: 52.0%, Ontario: 48.5%, and Saskatchewan: 28.5%) (Appendix 2, Table 17). There were also substantial differences in the proportion of new users identified in the US Merative MarketScan (17.0% in the postsurgical indication, 11.6% in the trauma indication, 26.6% in the dental indication, and 9.0% in the other pain indication) compared to the provincial datasets in Canada (5.4% to 40.3% for postsurgical indication, 5.6% to 8.5% for the trauma indication, and 3.5% to 9.0% for the other pain indication; Appendix 2, Tables 15 to 18).

## Person-Time and Incidence Rates

Table 3 shows the total intention-to-treat and as-treated person-time available for nonusers, new users, and prevalent users when implementing a 30-day grace period and using the landmark dates in the comparative safety analyses. As expected, the intention-to-treat person-time is much longer than the as-treated person-time for the new users and the prevalent users across every indication. The average as-treated follow-up after the landmark dates for new users in the postsurgical indication was 42.2 days, 27.6 days for the trauma indication, 31.2 days for the dental indication, and 34.4 days for the other pain indication, suggesting that most patients who filled a prescription during the landmark period did not begin sustained use of opioids

and initially received short supplies. Implementing a grace period whereby a gap equal to the days supply of the prescription does not result in censoring (e.g., a 7-day prescription requires another fill within 14 days) resulted in an even shorter average as-treated follow-up duration due to a number of patients who filled prescriptions during a 30-day landmark period following their indication but discontinued before the end of the landmark. The days supply length grace period was replaced with the 30-day grace period to limit this issue while also accounting for lingering biologic effects of opioids and the large disconnect between the recorded days supply and the practical days supply when taking opioids as needed for pain. Site-specific results are available in Appendix 2, Tables 19 to 23.

### Table 3: Intention-To-Treat and As-Treated Follow-Up Time by Indication and Exposure Group for the Feasibility Study

| Indication[a] and opioid users | Total N (%) | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| **Postsurgical** | | | |
| Nonusers | 24,869,997 (75.6) | 75,884,070 | 44,647,347 |
| New users | 5,989,535 (18.2) | 20,658,778 | 692,149 |
| Prevalent users | 2,018,696 (6.1) | 6,474,570 | 664,514 |
| **Trauma** | | | |
| Nonusers | 39,876,344 (84.5) | 122,972,283 | 78,685,862 |
| New users | 5,154,627 (10.9) | 15,797,677 | 389,282 |
| Prevalent users | 2,156,201 (4.6) | 6,630,706 | 1,496,708 |
| **Dental** | | | |
| Nonusers | 155,272 (56.9) | 449,446 | 305,290 |
| New users | 85,229 (31.2) | 317,016 | 7,285 |
| Prevalent users | 32,468 (11.9) | 114,634 | 22,596 |
| **Other pain** | | | |
| Nonusers | 49,415,999 (87.3) | 147,276,766 | 92,949,015 |
| New users | 4,855,920 (8.6) | 13,671,805 | 456,746 |
| Prevalent users | 2,303,814 (4.1) | 6,850,599 | 1,858,921 |

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

Table 4 presents the total intention-to-treat person-years, events, and pooled estimates of incidence rates from the feasibility analyses for the 2 outcomes ultimately selected for the comparative safety study (outcome 1, ED or inpatient encounter; outcome 2, inpatient encounter with CT scan) for each of the 4 indications. The rate of both outcomes varied across the different indication cohorts as one might expect given their differing age and comorbidity profile, with the dental indication cohort experiencing the lowest rates (19.2 per 10,000 person-years for outcome 1; 4.6 per 10,000 person-years for outcome 2), followed by the trauma cohort (24.6 for outcome 1; 5.2 for outcome 2), other pain indication cohort (25.2 for outcome 1 ; 5.5 for outcome 2), and the postsurgical cohort (29.0 for outcome 1; 6.6 for outcome 2). Other outcome

definitions that were explored either were too rare to analyze accurately in the individual databases (e.g., inpatient encounter with subsequent surgery or subsequent mortality) or would only be implementable in very few sites during the final analysis (e.g., ED encounter with CT scan). The decision was made to limit to the postsurgical, trauma, and other pain indications for the comparative safety analysis due to the low rates of the more severe outcome and the limited potential size of the dental indication cohort. Site-specific results are available in Appendix 2, Table 24.

### Table 4: Intention-to-Treat Crude Incident Rates of Diverticulitis by Indication and Outcome Definition for the Feasibility Study

| Indication[a] and outcome[b] | Total person-years | Total events | Incidence rate (per 10,000 person-years) |
|---|---|---|---|
| **Postsurgical** | | | |
| Outcome 1 | 103,017,419 | 298,868 | 29.0 |
| Outcome 2 | 99,260,800 | 65,370 | 6.6 |
| **Trauma** | | | |
| Outcome 1 | 145,400,667 | 357,060 | 24.6 |
| Outcome 2 | 139,595,347 | 72,209 | 5.2 |
| **Dental** | | | |
| Outcome 1 | 881,097 | 1,689 | 19.2 |
| Outcome 2 | 843,135 | 385 | 4.6 |
| **Other pain** | | | |
| Outcome 1 | 167,799,169 | 422,870 | 25.2 |
| Outcome 2 | 163,077,372 | 89,912 | 5.5 |

ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

[b]US Merative MarketScan data were not available for outcome 1; Manitoba data were not available for ED visits for outcome 1; and Saskatchewan data were not available for outcome 2.

## Cumulative Incidence Curves

Appendix 2, Figures 9 and 10 show the cumulative incidence curves for outcomes 1 and 2 for the first 2 years after the landmark date in Alberta, Ontario, Manitoba, and Saskatchewan in each of the postsurgical cohorts (combining all exposure groups) using the intention-to-treat follow-up. Cumulative incidence of outcome 1 appeared to vary considerably across sites, being considerably higher in Manitoba and Saskatchewan than in Alberta and Ontario (possibly due to coding differences or data available to each site). Conversely, the cumulative incidence of outcome 2 was fairly consistent across sites with no initial spike following the surgical procedure. Table 5 summarizes the averages (weighted by population size) of the 30-, 180-, and 730-day risks for outcome 1 and outcome 2 estimated across the various sites using life table approaches. Site-specific results are available in Appendix 2, Tables 25 to 29.

## Table 5: Weighted Average Risk of Diverticulitis by Indication and Outcome Definition for the Feasibility Study

| Indication[a] and outcome[b] | Average 30-day risk | Average 180-day risk | Average 730-day risk |
|---|---|---|---|
| **Postsurgical** | | | |
| Outcome 1 | 0.00026 | 0.00149 | 0.00546 |
| Outcome 2 | 0.00007 | 0.00034 | 0.00124 |
| **Trauma** | | | |
| Outcome 1 | 0.00014 | 0.00079 | 0.00310 |
| Outcome 2 | 0.00005 | 0.00026 | 0.00100 |
| **Dental** | | | |
| Outcome 1 | 0.00021 | 0.00091 | 0.00369 |
| Outcome 2 | 0.00004 | 0.00017 | 0.00082 |
| **Other pain** | | | |
| Outcome 1 | 0.00018 | 0.00094 | 0.00341 |
| Outcome 2 | 0.00005 | 0.00028 | 0.00108 |

ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

[b]US Merative MarketScan data were not available for outcome 1; Manitoba data were not available for ED visits for outcome 1; and Saskatchewan data were not available for outcome 2.

## Comparative Safety Study Cohort Sizes

Table 6 describes the participating sites and the sizes of the 3 indication cohorts in the comparative safety study.

## Table 6: Size of Indication Cohorts by Site for the Comparative Safety Study

| Site | Postsurgical N = 23,084,410 | Trauma N = 8,673,973 | Other pain N = 5,763,741 |
|---|---|---|---|
| Alberta | 652,539 | 2,521,960 | 2,870,663 |
| British Columbia | 1,515,904 | 3,090,060 | NA |
| Manitoba | 427,183 | 678,264 | 604,737 |
| Ontario | 1,552,222 | 1,744,602 | 1,712,489 |
| Saskatchewan | 446,859 | 639,087 | 575,852 |
| UK CPRD | 787,200 | NA | NA |
| US Merative MarketScan | 17,702,503 | NA | NA |

CPRD = Clinical Practice Research Datalink; NA = not applicable.

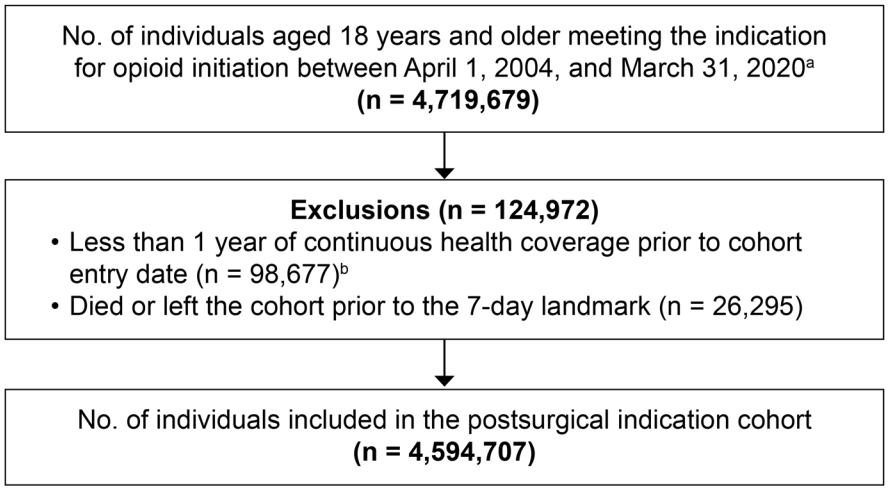
Note: British Columbia data were only available for the postsurgical and trauma indications. The UK CPRD and US Merative MarketScan data were for the postsurgical indication.

## Comparative Safety Study Results for the Postsurgical Indication Cohort

### Baseline Characteristics of the Comparative Safety Postsurgical Cohort

The comparative safety analysis included 23,084,410 individuals in the postsurgical indication cohort, including 4,594,707 from Canada; 787,200 from the UK CPRD; and 17,702,503 from the US Merative MarketScan. The study cohort construction for the 3 regions is presented in Figures 2 to 4.

### Figure 2: Flow Chart for Postsurgical Indication Study Cohort Construction in Canada

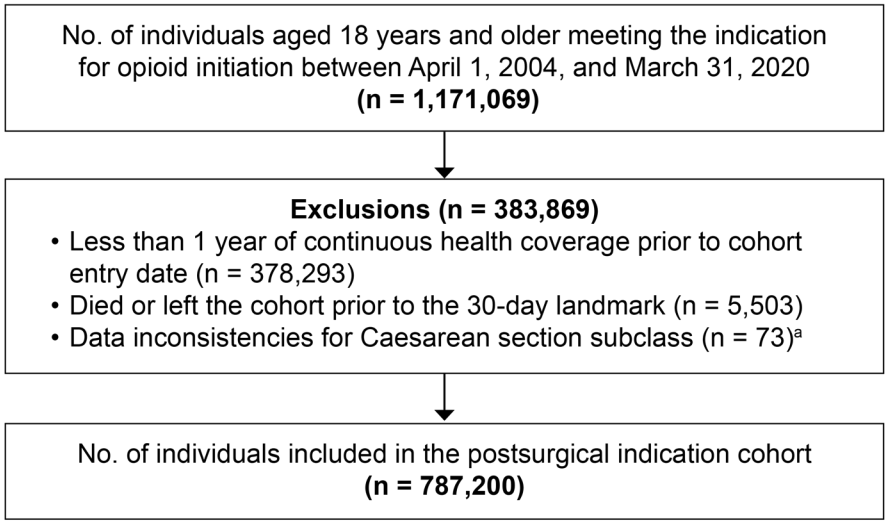



Note: Data aggregated for 5 provinces (Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan).

[a]Data were available as of 2008 for Alberta and 2013 for Ontario.

[b]Individuals with less than 365 days of health coverage before cohort entry date could not be identified in Alberta due to the unavailability of start of coverage date.

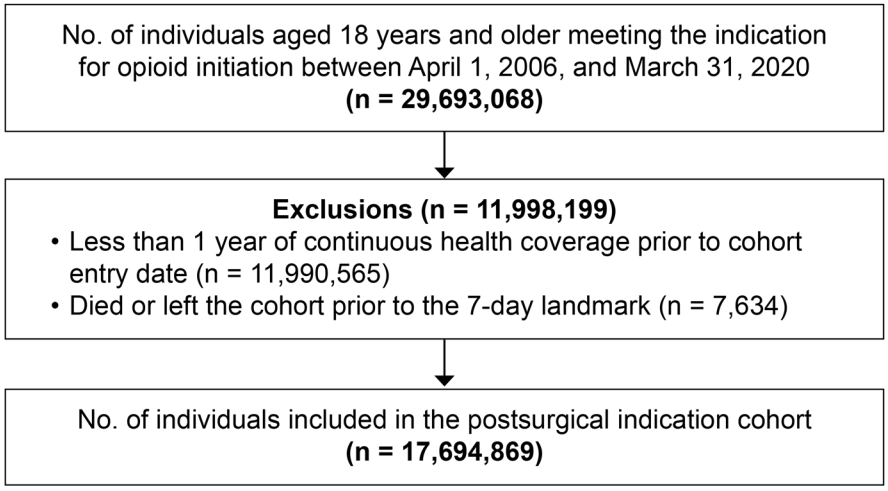
### Figure 3: Flow Chart for Postsurgical Indication Study Cohort Construction in UK CPRD




CPRD = Clinical Practice Research Datalink.

[a]An additional 73 individuals were excluded for the Caesarean section who were males, had dementia, or were aged 65 years and older.

## Figure 4: Flow Chart for Postsurgical Indication Study Cohort Construction in US Merative MarketScan




The distribution of key covariates between new users and nonusers before and after odds weighting is shown in Table 7 (refer to additional covariates in Appendix 3, Table 30). There was some variation between the underlying surgical indications between new users of opioids following surgery in the Canadian provinces (5.1% excision, 14.4% knee or hip replacement, 13.2% hernia repair, 6.7% Caesarean section, and 60.6% other surgery), the US Merative MarketScan (11.6% excision, 3.0% knee or hip replacement, 0.4% hernia repair, 16.0% Caesarean section, and 72.9% other surgery), and the UK CPRD (6.2% excision, 84.1% knee or hip replacement, 1.2% hernia repair, and 8.6% Caesarean section), with some of the deviation of the UK CPRD population due to the exclusion of the other surgery subclass.

The proportion of females (versus males) in the study varied across the Canadian provinces (54.9%), the US Merative MarketScan (62.4%), and the UK CPRD (59.0%), likely due to differences in the percentage of the indication with specific procedures (e.g., Caesarean section). The Canadian provincial cohort had a higher percentage of patients aged 65 years and older (19.4%) compared with the US Merative MarketScan cohort (7.3%) but lower than in the UK CPRD cohort (59.3%).

### Exposure Group Size

The percentage of patients that were new users of opioids within the 7-day landmark period differed across the Canadian provinces (31.2%), the US Merative MarketScan (18.1%), and the UK CPRD (9.7%), as did the percentage of patients with nonuse (62.2%, 75.6%, and 76.1%, respectively) and prevalent use (6.6%, 6.3%, and 14.1%, respectively). These differences may result from a variety of factors with the 3 most prominent being the type of database (general practitioner record in the UK CPRD versus insurance claims in the Canadian provinces and the US Merative MarketScan) and the substantial differences in the populations and surgical subclasses present within study population (with much lower rates of knee or hip replacement in the US Merative MarketScan, for example), and the differing time periods represented within each group.

### Differences in Baseline Characteristics Between New Users and Nonusers

New opioid users were younger at baseline than nonusers in the North American databases (patients aged 18 to 39 years in Canada: 33.3% versus 23.3%; patients aged 18 to 39 years in the US Merative MarketScan: 42.0% versus 24.9%), whereas this was the opposite in the UK CPRD (patients aged 18 to 39 years: 9.7% versus 23.9%). New users also appeared healthier at baseline than both nonusers and prevalent users in the Canadian and US cohorts; the proportion of patients with myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, diabetes, chronic obstructive pulmonary disease, or chronic kidney disease were all lower in the new users than the nonusers. The only indicator that was higher in the Canadian and US cohorts for the new users was current tumour (likely indicative of surgeries for the removal of tumours) and, in the US cohort, the proportion of patients with histories of diverticulosis or diverticulitis. Conversely, in the UK CPRD new users were generally less healthy than nonusers, likely due to the elimination of some indications from the CPRD cohort to account for data extraction restrictions. The CPRD data also does not include prescription data from specialists (except when the prescriptions ordered by the specialists are ordered again by the general practitioner). After applying odds weights (or IPTW, refer to Appendix 3, Table 32, depending on the analysis), SMDs in baseline characteristics between new users and nonusers, or new users and prevalent users (Appendix 3, Tables 31 and 32) were less than 0.100 for age categories, sex, and all comorbidities, suggesting a good balance between the groups.

## Main Findings

### Site Contributions

Differences in the data available to specific sites (as well as the overall cohort size in some provinces) resulted in some sites being unable to contribute to specific analyses. Table 1 in the data sources section summarizes these contributions. For the as-treated analyses, Alberta, Manitoba, Ontario, Saskatchewan, and the UK CPRD were able to contribute to the pooled analyses of outcome 1, while Alberta, British Columbia, Manitoba, Ontario, the US Merative MarketScan, and the UK CPRD were able to contribute to the pooled analyses of outcome 2. For the intention-to-treat analyses, every site other than the US Merative MarketScan and British Columbia were able to contribute to the pooled analyses of outcome 1, while every site except Saskatchewan were able to contribute to the pooled analyses of outcome 2.

## Table 7: Baseline Characteristics of Opioid New Users and Nonusers Before and After Odds Weighting for the Postsurgical Indication Cohort, by Region

| Characteristic (%) | Canada | | | UK CPRD | | | US Merative MarketScan[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 1,434,490 | Nonusers N = 2,858,751 | Nonusers N = 1,434,756 | New users N = 76,462 | Nonusers N = 599,417 | Nonusers N = 76,436 | New users N = 3,198,147 | Nonusers N = 13,382,299 | Nonusers N = 3,196,171 |
| **Calendar year of cohort entry[b]** | | | | | | | | | |
| 2004 to 2007 | 14.2 | 17.0 | 14.5 | 21.0 | 22.6 | 21.1 | 7.6 | 9.6 | 7.6 |
| 2008 to 2011 | 14.8 | 20.6 | 14.9 | 23.4 | 23.6 | 23.4 | 35.7 | 38.5 | 35.8 |
| 2012 to 2015 | 30.5 | 28.0 | 30.4 | 25.4 | 24.4 | 25.3 | 30.3 | 30.3 | 30.3 |
| 2016 to 2020 | 40.4 | 34.3 | 40.1 | 30.2 | 29.5 | 30.2 | 26.4 | 21.6 | 26.3 |
| **Age (years)** | | | | | | | | | |
| 18 to 39 | 33.3 | 23.3 | 33.7 | 9.7 | 23.9 | 9.7 | 42.0 | 24.9 | 41.4 |
| 40 to 64 | 47.3 | 36.7 | 47.0 | 31.0 | 30.2 | 30.9 | 50.6 | 58.9 | 51.2 |
| 65 to 79 | 16.9 | 29.5 | 16.8 | 46.8 | 30.8 | 46.7 | 6.2 | 12.0 | 6.2 |
| 80+ | 2.5 | 10.5 | 2.5 | 12.5 | 15.1 | 12.7 | 1.1 | 4.2 | 1.3 |
| **Sex** | | | | | | | | | |
| Males | 45.1 | 40.5 | 44.8 | 41.0 | 37.7 | 41.0 | 37.6 | 38.5 | 37.5 |
| Females | 54.9 | 59.5 | 55.2 | 59.0 | 62.3 | 59.0 | 62.4 | 61.5 | 62.5 |
| **Income quintile[c]** | | | | | | | | | |
| First (lowest) | 17.3 | 19.3 | 17.3 | 19.3 | 19.8 | 19.3 | — | — | — |
| Second | 19.1 | 19.5 | 19.0 | 18.5 | 18.3 | 18.4 | — | — | — |
| Third | 19.8 | 18.9 | 19.8 | 21.8 | 21.4 | 21.8 | — | — | — |
| Fourth | 20.3 | 17.9 | 20.3 | 20.9 | 20.6 | 20.9 | — | — | — |
| Fifth (highest) | 20.5 | 17.4 | 20.5 | 19.6 | 20.0 | 19.6 | — | — | — |

| Characteristic (%) | Canada | | | UK CPRD | | | US Merative MarketScan[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 1,434,490 | Nonusers N = 2,858,751 | Nonusers N = 1,434,756 | New users N = 76,462 | Nonusers N = 599,417 | Nonusers N = 76,436 | New users N = 3,198,147 | Nonusers N = 13,382,299 | Nonusers N = 3,196,171 |
| **Comorbidities** | | | | | | | | | |
| History of diverticulitis or diverticulosis | 2.0 | 2.4 | 2.1 | 11.4 | 8.2 | 11.4 | 1.5 | 1.1 | 1.5 |
| History of myocardial infarction | 2.4 | 7.4 | 2.5 | 4.2 | 3.4 | 4.2 | 0.5 | 0.6 | 0.5 |
| History of congestive heart failure | 1.3 | 4.4 | 1.4 | 4.7 | 4.3 | 4.6 | 0.6 | 1.0 | 0.6 |
| Peripheral vascular disease | 1.0 | 2.1 | 1.0 | 3.8 | 3.5 | 3.8 | 0.7 | 1.1 | 0.7 |
| Cerebrovascular accident | 1.0 | 2.6 | 1.1 | 5.1 | 4.6 | 5.1 | 1.2 | 1.8 | 1.2 |
| Chronic obstructive pulmonary disease | 3.8 | 6.2 | 3.8 | 5.7 | 4.5 | 5.7 | 2.8 | 3.7 | 2.8 |
| Diabetes mellitus | 10.2 | 16.6 | 10.2 | 12.3 | 8.6 | 12.2 | 7.9 | 10.8 | 7.9 |
| Chronic kidney disease | 1.3 | 3.1 | 1.3 | 10.8 | 9.7 | 10.8 | 0.8 | 1.4 | 0.8 |
| Current tumour | 13.0 | 12.3 | 14.2 | 11.7 | 13.7 | 11.7 | 7.3 | 5.0 | 7.4 |
| **Subclass of indication[d]** | | | | | | | | | |
| Common excision | 5.1 | 5.4 | 5.1 | 6.2 | 43.3 | 6.2 | 11.6 | 22.7 | 10.4 |
| Knee, hip, or shoulder surgery | 14.4 | 5.7 | 14.4 | 84.1 | 38.5 | 84.1 | 3.0 | 0.9 | 3.0 |

| Characteristic (%) | Canada | | | UK CPRD | | | US Merative MarketScan[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 1,434,490 | Nonusers N = 2,858,751 | Nonusers N = 1,434,756 | New users N = 76,462 | Nonusers N = 599,417 | Nonusers N = 76,436 | New users N = 3,198,147 | Nonusers N = 13,382,299 | Nonusers N = 3,196,171 |
| Hernia repair | 13.2 | 4.6 | 13.2 | 1.2 | 2.1 | 1.2 | 0.4 | 0.1 | 0.4 |
| Caesarean section | 6.7 | 11.0 | 6.7 | 8.6 | 16.1 | 8.6 | 16.0 | 2.7 | 14.3 |
| Other surgery | 60.6 | 73.4 | 60.7 | — | — | — | 72.9 | 74.3 | 72.9 |

CPRD = Clinical Practice Research Datalink.

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]The US Merative MarketScan cohort numbers were calculated before exclusion of the 7,634 patients who died or left the cohort before the landmark date from the analysis.

[b]Alberta data were available as of 2008, Ontario as of 2013, and the US Merative MarketScan as of 2006.

[c]Site-specific definition. Missing values not reported and account for discrepancies between income quintile categories and overall cohort totals. Data were not available in the US Merative MarketScan. Data were not reported for British Columbia, which was able to adjust for low income versus not low income (or missing) rather than quintiles.

[d]Other surgery subclass not included in the UK CPRD. Patients were allowed to enter multiple subclasses in the US Merative MarketScan.

### Diverticulitis Incidence Rates

Incidence rates of outcome 1 and outcome 2 among new users of opioids in the postsurgical indication cohort were low but did differ across provinces in both intention-to-treat and as-treated analyses (refer to Table 8). Notable differences include higher rates of outcome 1 in both the intention-treat and as-treated analyses in the UK CPRD (73.7 and 65.0 per 10,000 person-years) compared to the Canadian provinces overall (29.0 and 29.1 per 10,000 person-years). For outcome 2, higher rates were typically observed in the as-treated analyses (Canada overall: 6.7; UK CPRD: 2.8; US Merative MarketScan: 8.6 per 10,000 person-years) than in the intention-to-treat analyses (Canada overall: 3.5; UK CPRD: 0.9; US Merative MarketScan: 5.6 per 10,000 person-years). Notably, there were only a limited number of events (less than 6) in Alberta and the UK CPRD for the as-treated analyses for outcome 2. Differences were also noted across the Canadian provinces for both outcomes and analyses.

## Table 8: Crude Incidence Rates of Diverticulitis Among New Users by Outcome Definition and Follow-up for the Postsurgical Indication, by Region

| Outcome and follow-up | Total person-years | Total events | Crude incidence rate (per 10,000 person-years) |
|---|---|---|---|
| **Outcome 1, intention to treat** | | | |
| **Canada** | **5,773,301** | **16,759** | **29.0** |
| Alberta | 212,529 | 627 | 29.5 |
| Manitoba | 1,547,538 | 4,959 | 32.0 |
| Ontario | 3,307,272 | 7,829 | 23.7 |
| Saskatchewan | 705,962 | 3,344 | 47.4 |
| **UK CPRD** | **441,985** | **3,256** | **73.7** |
| **Outcome 1, as treated** | | | |
| **Canada** | **116,858** | **340** | **29.1** |
| Alberta | 4,122 | 21 | 51.0 |
| Manitoba | 14,854 | 35 | 23.6 |
| Ontario | 54,765 | 157 | 28.7 |
| Saskatchewan | 43,118 | 127 | 29.5 |
| **UK CPRD** | **14,466** | **94** | **65.0** |
| **Outcome 2, intention to treat** | | | |
| **Canada** | **8,989,368** | **3,125** | **3.5** |
| Alberta | 212,529 | 61 | 2.9 |
| British Columbia | 3,922,029 | 705 | 1.8 |
| Manitoba | 1,547,538 | 878 | 5.7 |
| Ontario | 3,307,272 | 1,481 | 4.5 |
| **UK CPRD** | **455,254** | **41** | **0.9** |

| Outcome and follow-up | Total person-years | Total events | Crude incidence rate (per 10,000 person-years) |
|---|---|---|---|
| **US Merative MarketScan** | **9,642,869** | **5,360** | **5.6** |
| **Outcome 2, as treated** | | | |
| **Canada** | **118,015** | **79** | **6.7** |
| Alberta | S | S | 2.4 |
| British Columbia | 44,275 | 11 | 2.5 |
| Manitoba | 14,854 | 9 | 6.1 |
| Ontario | 54,765 | 56 | 10.2 |
| **UK CPRD** | **S** | **S** | **2.8** |
| **US Merative MarketScan** | **278,568** | **240** | **8.6** |

CPRD = Clinical Practice Research Datalink; ED = emergency department; S = value suppressed.

Notes: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

Manitoba data were not available for ED visits for outcome 1.

Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

### As-Treated Analyses: Crude Associations Between New Users and Nonusers

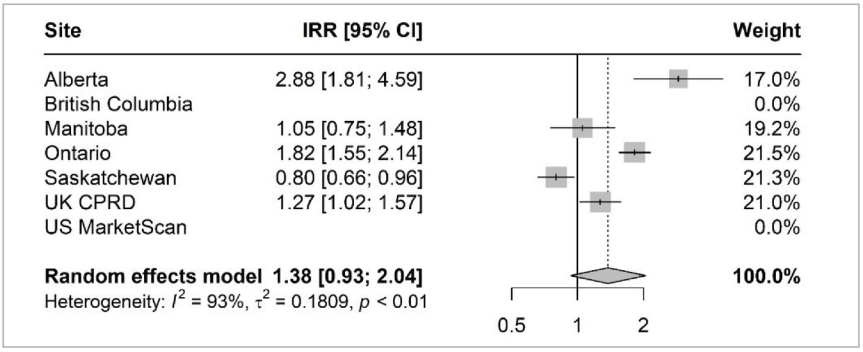
The direction of the crude as-treated association between new use (versus nonuse) and the rate of outcome 1 varied across Canadian provinces (Alberta IRR = 2.85; Manitoba IRR = 0.72; Ontario IRR = 1.51; and Saskatchewan IRR = 0.88) and the UK CPRD (IRR = 1.80), possibly due to differences in sustained use of opioids and the characteristics of each population.

Conversely, for outcome 2 the direction of the crude as-treated association was consistent: new users had higher rates of outcome 2 than nonusers across the Canadian provinces (Alberta IRR = 1.34; British Columbia IRR = 1.78; Manitoba IRR = 1.21; and Ontario IRR = 2.56), the US Merative MarketScan (IRR = 1.57), and the UK CPRD (IRR = 4.54), though the UK CPRD association was farther from the null than any of the other sites.

### As-Treated Analyses: New Users Versus Odds-Weighted Nonusers

After weighting with both odds weights and IPCW, the pooled IRR for outcome 1 was 1.38 (95% CI, 0.93 to 2.04), suggesting a small but not statistically significant increase in diverticulitis risk with sustained new use of opioids compared to nonuse (Figure 5) that was primarily driven by results in Alberta, Ontario, and the CPRD. The IRR was similar when including only the Canadian provinces in the analysis (IRR = 1.42; 95% CI, 0.83 to 2.42). There was considerable heterogeneity in the outcome; however, with an $I^2$ value of 93%, largely due to the results in Saskatchewan being on the opposite side of the null compared to the other sites and Manitoba being centred on the null, suggesting that outcome 1 may not represent a uniform concept across sites. The corresponding pooled IRD in the full data of 7.97 events per 10,000 person-years (95% CI, −2.98 to 18.92) was also not statistically significant, with substantial heterogeneity ($I^2$ = 90%) with larger IRDs in Alberta (31.20), Ontario (12.86), and the UK CPRD (13.19) compared to Manitoba (1.16) and estimates on the other side of the null in Saskatchewan (−7.37). The IRD of only the Canadian data were 6.95 events per 10,000 person-years (95% CI, −5.67 to 19.57), similar to the full results.

## Figure 5: Forest Plot for the As-Treated Results in Outcome 1 for New Users Versus Nonusers for the Postsurgical Indication Cohort




CI = confidence interval; CPRD = Clinical Practice Research Datalink; ED = emergency department; IRR = incidence rate ratio.

Notes: Confidence limits in the plot are based on standard errors derived from the bootstrapped CIs supplied by each site.

Outcome 1 is ED or inpatient visits for diverticulitis only.

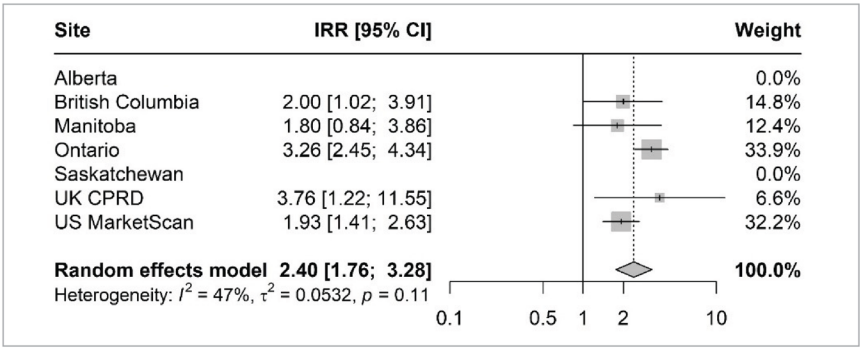
Data were not available for British Columbia and the US Merative MarketScan.

Results for outcome 2 are shown in Figure 6. The pooled IRR was statistically significant (pooled IRR = 2.40; 95% CI, 1.76 to 3.28) with some heterogeneity ($I^2$ = 47%) and the corresponding IRD was statistically significant despite its low magnitude (pooled IRD = 3.36 per 10,000 person-years; 95% CI, 1.19 to 5.52) with more heterogeneity ($I^2$ = 71%). Canada-only results were similar, though the IRD was not statistically significant due to the smaller amount of data (pooled IRR = 2.57; 95% CI, 1.72 to 3.82; pooled IRD per 10,000 person-years = 3.62; 95% CI, −0.23 to 7.48). The difference in statistical significance is primarily the result of more heterogeneity on the ratio scale than the difference scale.

Note: The scale of the x-axes for the forest plots varies across figures.

The association between new use and 30-day diverticulitis risk was small and statistically significant on the relative scale (outcome 1 pooled RR = 1.20; 95% CI, 1.01 to 1.44 and outcome 2 pooled RR = 1.38; 95% CI, 1.03 to 1.86) and almost statistically significant on the absolute scale (outcome 1 pooled RD = 0.0041%; 95% CI, −0.0002% to 0.0084% and outcome 2 pooled RD = 0.0011%; 95% CI, −0.0002% to 0.0023%) scales, with very little heterogeneity in the RR or RDs ($I^2$ = 0% for both RRs and RDs for both outcomes).

## Figure 6: Forest Plot for the As-Treated Results in Outcome 2 for New Users Versus Nonusers for the Postsurgical Indication Cohort




CI = confidence interval; CPRD = Clinical Practice Research Datalink; IRR = incidence rate ratio.

Notes: Confidence limits in the plot are based on standard errors derived from the bootstrapped CIs supplied by each site.

Outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

Data were not available in Saskatchewan and not included for Alberta due to the limited number of events resulting in overly precise confidence limits.

At 730 days, the pooled estimate of the RR was consistent with the overall estimate of the IRR for both outcomes (outcome 1 pooled RR = 1.37; 95% CI, 0.92 to 2.04 and outcome 2 RR = 2.22; 95% CI, 1.08 to 4.54), with the greater variance of the 730-day risks the result of low numbers of new users sustaining opioid use for 2 years following surgery resulting in a lack of precision. The pooled estimate of the 730-day RD was not statistically significant for either outcome (outcome 1 pooled RD = 0.153%; 95% CI, −0.085% to 0.390% and outcome 2 RD = 0.0246%; 95% CI, −0.0373% to 0.0865%), though Alberta and the UK CPRD estimates were not included in the RD analysis due to inaccurate CI widths due to the low number of events and loss to as-treated follow-up.

### Intention-To-Treat Analyses: Crude Associations Between New Users and Nonusers

The crude intention-to-treat association between new use (versus nonuse) and the rate of outcome 1 was generally similar across Canadian provinces (Alberta IRR = 0.93; Manitoba IRR = 0.81; Ontario IRR = 0.98; and Saskatchewan IRR = 0.92) but the UK CPRD data had an association on the opposite side of the null (UK CPRD IRR = 1.52), likely as a result of the older age and generally poorer health of new users compared to nonusers.

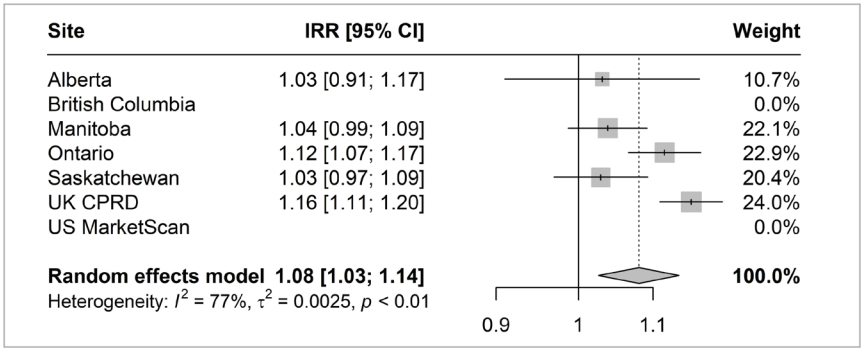
Outcome 2 exhibited less heterogeneity than outcome 1 with IRRs between 0.78 (Manitoba) and 0.95 (UK CPRD) across the sites. While this may indicate that more severe diverticulitis is less correlated with the factors that differ across data partners, it may also simply be the result of a less common outcome resulting in more variable treatment effect estimates due to chance.

### Intention-To-Treat Analyses: New Users Versus Odds-Weighted Nonusers

The pooled intention-to-treat IRR for outcome 1 (odds-weighted nonusers to new users) was 1.08 (95% CI, 1.03 to 1.14) (Figure 7) with a corresponding IRD of 3.10 per 10,000 person-years (95% CI, 0.59 to 5.62), suggesting a small but statistically significant association between initiating opioids within 7 days following surgery and diverticulitis. The relative results were similar in the Canada-only analysis, though the IRD was even closer to the null (IRR = 1.06; 95% CI, 1.01 to 1.11 and IRD = 1.97 per 10,000 person-years; 95% CI, 1.17 to 2.77).

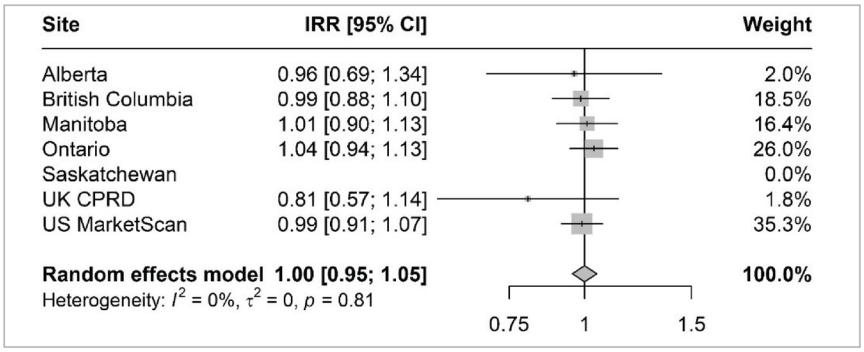
The intention-to-treat IRR for outcome 2 (Figure 8) was null (IRR = 1.00; 95% CI, 0.95 to 1.05). The IRD was also not statistically significant (−0.04 per 10,000 person-years; 95% CI, −0.19 to 0.10). Similar results were observed in the Canada-only analysis of outcome 2 (IRR = 1.01; 95% CI, 0.95 to 1.07). The 30-day RRs for outcome 1 (RR = 1.09; 95% CI, 0.92 to 1.30) and outcome 2 (RR = 1.16; 95% CI, 0.89 to 1.52) were similar to the as-treated RRs in magnitude but were not statistically significant. The RRs at day 730 were similar to the IRRs (pooled IRR for outcome 1 of 1.09; 95% CI, 1.04 to 1.14 and pooled IRR for outcome 2 of 0.95; 95% CI, 0.88 to 1.04), just as they were in the as-treated analyses.

## Figure 7: Forest Plot for the Intention-To-Treat Results in Outcome 1 for New Users Versus Nonusers for the Postsurgical Indication Cohort




CI = confidence interval; CPRD = Clinical Practice Research Datalink; ED = emergency department; IRR = incidence rate ratio.
Notes: Confidence limits in the plot are based on standard errors derived from the bootstrapped CIs supplied by each site.
Outcome 1 is ED or inpatient visits for diverticulitis only.
Data were not available for British Columbia and US Merative MarketScan.

## Figure 8: Forest Plot for the Intention-To-Treat Results in Outcome 2 for New Users Versus Nonusers for the Postsurgical Indication Cohort




CI = confidence interval; CPRD = Clinical Practice Research Datalink; IRR = incidence rate ratio.
Notes: Confidence limits in the plot are based on standard errors derived from the bootstrapped CIs supplied by each site.
Outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.
Data were not available for Saskatchewan.

### As-Treated Analyses: New Users Versus Odds-Weighted Prevalent Users

Baseline characteristics for new users and prevalent users before and after odds weighting are presented in Appendix 3, Table 31. After weighting and pooling, new sustained use of opioids (versus continued prevalent use) appeared to be associated with a lower rate of outcome 1 in the as-treated analyses (IRR for outcome 1 = 0.90; 95% CI, 0.76 to 1.05). There was some heterogeneity ($I^2$ = 45%) between the sites: estimates from Alberta (IRR = 1.17) and Ontario (IRR = 1.10) were on the opposite side of the null compared to the other sites (Manitoba IRR = 0.70; Saskatchewan IRR = 0.80; and UK CPRD IRR = 0.86).

For outcome 2, the pooled IRR was 1.12 (95% CI, 0.70 to 1.80) with more heterogeneity ($I^2$ = 63%), suggesting new users and prevalent users had similar rates overall. There was disagreement in the direction of this association across sites; however, with Ontario (IRR = 1.73) and the UK CPRD (IRR = 2.42) suggesting an increase in diverticulitis incidence rates among new users relative to prevalent users while Alberta (IRR = 0.57), British Columbia (IRR = 0.70), and the US Merative MarketScan (IRR = 0.79) were more suggestive of a lower rate in new users and Manitoba (IRR = 0.97) suggested no association.

### Intention-To-Treat Analyses: New Users Versus Odds-Weighted Prevalent Users

After odds weighting and pooling, new use of opioids (versus prevalent use) was also associated with lower rates of both outcomes in the intention-to-treat analysis (pooled IRR for outcome 1 = 0.90; 95% CI, 0.81 to 1.00 and pooled IRR for outcome 2 = 0.74; 95% CI, 0.69 to 0.80). There was much more heterogeneity in the analysis of outcome 1 ($I^2$ = 88%) than in outcome 2 ($I^2$ = 0%). This adds further support to the idea of differences in opioid use between the different sites as well as the notion that biases associated with prevalent users away from the null would arise if prevalent users and new users are included in a single exposure category and treated as having identical diverticulitis risk.

### Inverse Probability Weighted Analyses

The IPTW analyses that were pooled included Manitoba, Ontario, Saskatchewan, and the UK CPRD for outcome 1 and Manitoba, Ontario, and the UK CPRD for outcome 2. Baseline characteristics of new users, nonusers, and prevalent users before and after IPTW weighting are presented in Appendix 3, Table 32.

The pooled as-treated IPTW IRRs estimating the association between new use versus nonuse of opioids in the full population with IPTW were almost identical to those from the odds-weighted IRR estimating the treatment effect in new users (outcome 1 IRR = 1.35; 95% CI, 1.07 to 1.70 and outcome 2 IRR = 2.46, 95% CI, 1.37 to 4.41). The IRDs were also generally similar or slightly larger (outcome 1 IRD = 10.92 per 10,000 person-years; 95% CI, 6.56 to 15.29 and outcome 2 IRD = 3.37; 95% CI, −0.42 to 7.16), though the limited number of sites and events within those sites meant the outcome 2 results were not statistically significant. This suggests limited difference in the association of continuous opioid use with diverticulitis between new users and the rest of the study population.

While the pooled IPTW intention-to-treat estimates for outcome 1 were quite similar to the odds-weighted estimates (IRR = 1.13; 95% CI, 1.10 to 1.16 and IRD = 4.81 per 10,000 person-years; 95% CI, 2.47 to 7.16), the pooled IPTW intention-to-treat estimates for outcome 2 were actually on the other side of the null from the odds-weighted estimates (IRR = 1.08; 95% CI, 1.00 to 1.16 and IRD = 0.17 per 10,000 person-years; 95% CI, −0.35 to 0.70).

### Subgroup Analyses

The expected increase in variation when conducting multiple comparisons and stratifying results into specific groups can lead to difficulty in interpretation of subgroup results. Given the potential dangers of severe diverticulitis events, its overall greater specificity, and the stronger association between these events and sustained opioid use in the main results of the comparative effectiveness study, the reporting here will focus

on the as-treated new users versus odds-weighted nonusers analyses of outcome 2. Results for the main and subgroup analyses are summarized in Table 9.

The pooled IRR was statistically significant in males (pooled IRR = 2.09; 95% CI, 1.58 to 2.78) and females (pooled IRR = 2.66; 95% CI, 1.62 to 4.36), though there was less variability between sites in males ($I^2$ = 0%) than in females ($I^2$ = 65%). IRDs were statistically significant for both males and females (pooled IRD in males = 3.47 per 10,000 person-years; 95% CI, 0.89 to 6.04 and pooled IRD in females = 3.48 per 10,000 person-years; 95% CI, 0.96 to 6.00), though both IRDs showed significant variability due to the differing baseline outcome rates at each site.

Three of the surgery subclasses (Caesarean section, hernia, and common excision) were not able to be analyzed as independent subgroups due to limited sample size within each of the individual sites. The hip and knee surgery subclass had a similar pooled IRR to the full postsurgical population (IRR in hip and knee = 2.44; 95% CI, 1.29 to 4.58) and a similar IRD as well (IRD in hip and knee = 3.31 per 10,000 person-years; 95% CI, −0.57 to 7.19). The other surgery category also had a similar IRR to the full population (IRR in other surgery = 2.36; 95% CI, 1.64 to 3.38) and a slightly higher IRD (IRD in other surgery = 3.79 per 10,000 person-years; 95% CI, 1.16 to 6.42) that was statistically significant.

While there were too few individuals aged 18 to 39 years to draw meaningful conclusions for any individual site, the IRR in those aged 40 to 64 years (IRR = 2.24; 95% CI, 1.75 to 2.88) was slightly greater than the IRR in individuals aged 65 years and older (IRR = 1.99; 95% CI, 1.00 to 3.95). The IRD, on the other hand, was greater in those aged 65 years and older (IRD = 4.20 per 10,000 person-years; 95% CI, −0.84 to 9.24) than those aged 40 to 64 years (IRD = 3.61 per 10,000 person-years; 95% CI, 1.90 to 5.33). The limited precision of the estimates in the 65 years and older age group is largely due to the lack of employer-insured individuals aged 65 years and older contributing to the US Merative MarketScan. Notably, the IRR (4.45) and IRD (18.41) in those aged 65 years and older in Ontario were much larger than in British Columbia (IRR = 1.10, IRD = 0.23), Manitoba (IRR = 1.13, IRD = 0.85), the UK CPRD (IRR = 2.92, IRD = 2.07), or the US Merative MarketScan (IRR = 1.40, IRD = 4.41), resulting in considerable variability in the IRR ($I^2$ = 70%) and the IRD ($I^2$ = 72%).

### Table 9: Summary of Results for As-Treated New Users Versus Odds-Weighted Nonusers Subgroup Analyses for Outcome 2 for the Postsurgical Indication

| Analysis | IRR (95% CI) | IRD per 10,000 person-years (95% CI) |
|---|---|---|
| **Main as-treated odds-weighted analysis** | **2.34 (1.66 to 3.30)** | **3.29 (1.16 to 5.42)** |
| Canada only | 2.57 (1.72 to 3.82) | 3.62 (−0.23 to 7.48) |
| **Sex** | | |
| Males | 2.09 (1.58 to 2.78) | 3.47 (0.89 to 6.04) |
| Females | 2.66 (1.62 to 4.36) | 3.48 (0.96 to 6.00) |
| **Age** | | |
| 40 to 64 years | 2.24 (1.75 to 2.88) | 3.61 (1.90 to 5.33) |

| Analysis | IRR (95% CI) | IRD per 10,000 person-years (95% CI) |
|---|---|---|
| ≥ 65 years | 1.99 (1.00 to 3.95) | 4.20 (−0.84 to 9.24) |
| **Subclass of indication** | | |
| Knee, hip, or shoulder surgery | 2.44 (1.29 to 4.58) | 3.31 (−0.57 to 7.19) |
| Other surgery | 2.36 (1.64 to 3.38) | 3.79 (1.16 to 6.42) |

CI = confidence interval; IRD = incidence rate difference; IRR = incidence rate ratio.

Notes: Outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

Data were available for British Columbia, Manitoba, Ontario, UK CPRD, and the US Merative MarketScan.

Results were not available for patients aged 18 to 39 years, and for Caesarean section, hernia, and common excision subclasses of indications subgroups due to limited sample size.

### Sensitivity Analyses

Sensitivity analyses were also focused on odds-weighted analyses comparing new users and nonusers. The as-treated results for outcome 2 (pooled IRR = 2.39; 95% CI, 1.53 to 3.74) were consistent with the original IRR of 2.34 when we excluded those with prescriptions for opioid maintenance therapy from the new user group, suggesting limited bias from these patients being prevalent users before experiencing their surgical indication.

The intention-to-treat results for outcome 2 when excluding nonusers with any opioid fill during the lookback period (pooled IRR excluding those nonusers = 1.05; 95% CI, 1.00 to 1.11) were slightly greater than the original IRR of 1.00, though the shift in estimate was heterogeneous with the point estimate becoming slightly greater in British Columbia, Manitoba, and the US Merative MarketScan and slightly lower in Ontario. However, all new site-specific estimates fell within the confidence limits of the prior ones. This suggests that the potential bias from including these patients as nonusers is limited and could not completely account for the magnitude of the observed as-treated estimates.

Finally, 4 of the data partners (Manitoba, Ontario, Saskatchewan, and the UK CPRD) examined whether recalculating weights within each bootstrap iteration would have a substantial impact on the upper and lower confidence limits for the as-treated outcome 1 and outcome 2 analyses. There were only minor changes in the width of their CIs in these sensitivity analyses. For example, lower confidence limit of 2.36 and upper confidence limit of 4.19 in the original analysis were of 2.38 and 4.03, respectively, in the analysis recalculating within each bootstrap iteration in Ontario (with the difference compared to the figures resulting from the averaging of the CI width to generate the standard errors before meta-analysis).

## Comparative Safety Study Results for the Trauma Indication Cohort

### Main Findings

#### As-Treated Analyses: New Users Versus Odds-Weighted Nonusers

The cohort construction for the trauma indication is depicted in Appendix 4, Figure 11. Data were available for Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan. A total of 8,673,973 individuals were included in this cohort. Baseline characteristics are presented in Appendix 4, Tables 33 and 34. After applying odds weights (or IPTW), covariates were well balanced between exposure groups. The crude incidence rates

of outcome 1 and outcome 2 for the as-treated and intention-to-treat analyses are presented in Appendix 4, Table 37. The lack of events in Alberta prevented them from contributing to subsequent analyses.

The relative scale as-treated association between new use versus nonuse of opioids and outcome 1 including Alberta, Manitoba, Ontario, and Saskatchewan was roughly the same as in the postsurgical cohort (pooled IRR = 1.61; 95% CI, 0.99 to 2.64). There was considerable heterogeneity ($I^2$ = 72%); however, as a result of Saskatchewan showing a null or protective association (IRR = 0.86; 95% CI, 0.65 to 1.14) while the other provinces showed harmful associations (Alberta IRR = 1.90; 95% CI, 1.34 to 2.67; Manitoba IRR = 1.95; 95% CI, 1.24 to 3.06; Ontario IRR = 2.27; 95% CI, 1.50 to 3.46). However, the absolute scale association was slightly higher than in the postsurgical cohort (pooled IRD = 9.73; 95% CI, −1.79 to 21.25).

When examining outcome 2 and using data from British Columbia, Manitoba, and Ontario, the association was stronger on the relative scale in comparison to the postsurgical results (pooled IRR = 3.96; 95% CI, 2.44 to 6.43), with no evidence of heterogeneity ($I^2$ = 0%). The association was also higher than the postsurgical estimate on the absolute scale (pooled IRD = 5.78; 95% CI, −0.64 to 12.19), albeit not statistically significant, and with evidence of heterogeneity ($I^2$ = 69%) due to differing baseline rates in outcome 2 across the different sites. While the stronger relative scale association may be the result of differences in patient characteristics, it may also be the result of greater selection bias resulting from heterogeneity between patients who maintain opioid use after a trauma indication versus a postsurgical indication.

### Intention-to-Treat Analyses: New Users Versus Odds-Weighted Nonusers

The intention-to-treat estimates were closer to the estimates in the postsurgical cohort than the as-treated ones (outcome 1 pooled IRR = 1.10; 95% CI, 1.03 to 1.19; outcome 2 pooled IRR = 1.21; 95% CI, 1.12 to 1.31), with IRDs even closer to the null (outcome 1 pooled IRD = 2.42 per 10,000 person-years; 95% CI, 0.64 to 4.21; outcome 2 pooled IRD = 0.53; 95% CI, 0.22 to 0.84), yet all 4 estimates were statistically significant.

### Subgroup Analyses

Manitoba and Ontario were able to examine the as-treated association between new use of opioids (versus nonuse) and outcome 2 in several subgroups within the trauma indication cohort. The relative scale associations in males (pooled IRR in males = 4.48; 95% CI, 1.76 to 11.43) and females (pooled IRR in females = 3.58; 95% CI, 1.28 to 10.00) were both elevated compared to the association in the postsurgical cohort, which is similar to the overall findings.

The indication subclasses were sufficiently large to examine in Ontario and Manitoba were sprains, strains, and fractures as well as burns and wounds. The pooled relative association in the sprains, strains, and fractures subgroup (pooled IRR in sprains, strains, and fractures = 2.79; 95% CI, 1.19 to 6.55) was very similar to the estimate from the postsurgical cohorts, though the absolute association was higher (pooled IRD in sprains, strains, and fractures = 6.40 per 10,000 person-years; 95% CI, −1.75 to 14.54), with no evidence of heterogeneity ($I^2$ = 0%). The burns and wounds subgroup had a greater relative association (pooled IRR in burns and wounds = 4.70; 95% CI, 1.08 to 20.41) driven by a large but imprecise association observed in Manitoba (IRR = 10.54; 95% CI, 3.60 to 30.86) that translated to some evidence of heterogeneity ($I^2$ = 81%).

This also resulted in a very imprecise estimate of the absolute association among these patients (pooled IRD in burns and wounds = 13.52; 95% CI, −14.32 to 42.16).

There were still too few patients within the trauma indication cohort to conduct analyses within the subgroup of patients aged 18 to 39 years. In patients aged 40 to 64 years, the pooled relative scale association was larger than that in the postsurgical cohort (pooled IRR in patients aged 40 to 64 years = 4.25; 95% CI, 2.14 to 8.44) with no evidence of heterogeneity between Ontario and Manitoba ($I^2$ = 0%). The absolute scale association when pooling was also stronger than the postsurgical cohort (pooled IRD in those aged 40 to 64 years = 9.16; 95% CI, −2.81 to 21.13). Estimates in patients aged 65 years and older included slightly lower IRRs (pooled IRR in those aged 65 years and older = 3.11; 95% CI, 1.53 to 6.31) with no evidence of heterogeneity ($I^2$ = 0%) and slightly higher IRDs (pooled IRD in those aged 65 years and older = 12.57; 95% CI, 0.36 to 24.78) also with no evidence of heterogeneity ($I^2$ = 0%).

## Comparative Safety Study Results for the Other Pain Indication Cohort

### Main Findings

#### As-Treated Analyses: New Users Versus Odds-Weighted Nonusers

A total of 5,763,741 individuals were included in the other pain indication cohort (Appendix 4, Figure 12). Data are available for Alberta, Manitoba, Ontario, and Saskatchewan. Baseline characteristics are presented in Appendix 4, Tables 35 and 36, and were well balanced after weighting (odds or IPTW). Appendix 4, Table 37 presents the crude incidence rates of outcome 1 and outcome 2 for the as-treated and intention-to-treat analyses.

Analyses for the other pain indication using data from Alberta, Manitoba, Ontario, and Saskatchewan were closer to the findings within the trauma cohort than the postsurgical cohort. The as-treated estimates on the ratio scale for outcome 1 (pooled IRR = 1.61; 95% CI, 1.10 to 2.35) were roughly the same as in the trauma and postsurgical cohorts, with substantial heterogeneity observed between the provinces ($I^2$ = 76%), though was statistically significant. However, the pooled IRD was slightly higher than either of the other indication cohorts (pooled IRD = 12.49; 95% CI, 2.81 to 22.17 per 10,000 person-years).

The estimated relative scale association between new use versus nonuse of opioids and outcome 2 using data from Ontario and Manitoba was closer to the association in the trauma cohort than the association in the postsurgical cohort (pooled IRR = 4.38; 95% CI, 2.44 to 7.85). The absolute scale association (pooled IRD = 11.08 events per 10,000 person-years; 95% CI, 0.38 to 21.79) was higher than either of the other cohorts; however, albeit with substantial heterogeneity ($I^2$ = 67%). Just as in the trauma indication cohort, these differences could be the result of greater selection bias in the other pain cohort than in the postsurgical cohort.

#### Intention-to-Treat Analyses: New Users Versus Odds-Weighted Nonusers

The intention-to-treat estimates were again close to the estimates in the postsurgical cohort (outcome 1 IRR = 1.07; 95% CI, 0.95 to 1.20; outcome 2 RR = 1.09; 95% CI, 1.00 to 1.18), though with IRDs even closer to

the null (outcome 1 IRD = 1.92 per 10,000 person-years; 95% CI, −1.54 to 5.39 and outcome 2 IRD = 0.37; 95% CI, −0.01 to 0.74) and not statistically significant.

### Subgroup Analyses

Manitoba and Ontario were both able to examine the as-treated association between new use of opioids (versus nonuse) and outcome 2 in several subgroups within the other indication cohort. The relative scale association in males was very similar to the postsurgical cohort (pooled IRR in males = 2.94; 95% CI, 1.77 to 4.91) while the relative scale association in females was closer to the trauma indication cohort (pooled IRR in females = 4.73; 95% CI, 2.06 to 10.86).

The only indication subclass where Manitoba and Ontario were able to conduct subgroup analyses was migraine and headache. The relative scale association in these patients was similar to the association in the full other indication cohort (pooled IRR in the migraine indication = 4.20; 95% CI, 1.24 to 14.18), with a similar absolute scale association to the overall cohort (pooled IRD in the migraine indication = 11.91; 95% CI, −4.64 to 28.46) with considerable variability due to the heterogeneity between the estimates (Ontario IRD = 21.19 versus Manitoba IRD = 4.23; $I^2$ = 72%).

The relative scale association in patients aged 65 years and older was elevated compared to the full other indication cohort (pooled IRR in those aged 65 years and older = 3.99; 95% CI, 2.46 to 6.49), with an absolute scale association much stronger than the rest of the other indication cohort (pooled IRD in those aged 65 years and older = 25.58; 95% CI, 10.01 to 41.15). The pooled relative association in patients aged 40 to 64 years was closer to the null (pooled IRR in patients aged 40 to 64 years = 2.72; 95% CI, 1.21 to 6.12) and the pooled absolute scale association was actually slightly lower than the full other indication cohort (pooled IRD in patients aged 40 to 64 years = 8.35; 95% CI, −0.13 to 16.82).

A summary table of the main results for the 3 indication cohorts is available in Appendix 5, Table 38.

## Strengths and Limitations

This study has a number of unique strengths. First, to our knowledge, this is the largest cohort study evaluating the association between new use of opioids and diverticulitis risk to date. Second, by focusing on cohorts of patients with an indication for opioid use, the potential for protopathic bias caused by patients initiating opioids to treat abdominal pain was minimized without conditioning on a potential mediator between opioid use and diverticulitis. Third, unlike past studies that employed case–control methods, we were able to estimate IRRs, IRDs, RRs, and RDs (key parameters of public health interest) and clearly separate new users of opioids from prevalent users (which may differ fundamentally from one another in terms of diverticulitis risk). Fourth, conducting both as-treated and intention-to-treat analyses identified whether initiation or sustained opioid use was associated with diverticulitis risk. Fifth, we were also able to assess whether our findings were consistent across different indications for opioid use with different susceptibility to various forms of biases. Finally, the large size of the study cohorts allowed the investigation of differences in

treatment effect estimates across different types of indications as well as some specific subgroups of interest to help understand potential factors that might modify the effect of opioid use on diverticulitis.

The central limitation of the pooled intention-to-treat analyses is the potential for residual confounding when comparing opioid users and nonusers. While we were able to balance a broad swathe of covariates associated with general health status as well as risk factors for diverticulitis, we did not account for confounding by concomitant medications like steroids, nonsteroidal anti-inflammatory drugs, and antibiotics (which may vary even with surgical subclasses), nor were we able to account for any confounding resulting from differential alcohol use or differential in-hospital opioid use (which also may vary even within surgical subclasses). Moreover, by conducting a new user versus nonuser comparison, rather than a user versus nonuser comparison, the potential for residual confounding by exposure history or biases associated with prevalent users was eliminated. The fact that the intention-to-treat results were close to the null (as expected with such high rates of discontinuation) is consistent with limited baseline confounding between new users and nonusers of opioids. That said, intention-to-treat estimates may not be generalizable to other populations that have different patterns of adherence and persistence (e.g., those initiating opioids for chronic pain), limiting their broader applicability. If almost everyone discontinues the treatment, or most of the population who does not initiate by day 7 eventually begins using it, the comparison can also become less useful.

To help combat this limitation, the as-treated analyses required patients to maintain opioid use (or nonuse) after the initial landmark period. While this approach ensures we are only treating patients using opioids as exposed during windows where they are likely to be physically exposed to the drug and when a link between opioid use and diverticulitis is most biologically plausible, the fact that some individuals are censored from the analysis and that those individuals may have a differing risk of the outcome can potentially generate selection bias. In the case of this specific study, this type of bias may lead to overestimation of the risk of diverticulitis if the new users who continue using opioids are older and less healthy or more susceptible to diverticulitis than those who do not. While IPCW was used to control this potential source of bias, only baseline covariates were used in the censoring models; any changes in the patients' status over time that may predict their continued use or nonuse of opioids were not captured. For example, the inability to capture postsurgical complications in the censoring weights which may be strongly associated with lack of mobility (and thus, constipation and potential diverticulitis) could bias results.

It is also important to note the substantial heterogeneity observed between the sites in a number of our primary analyses for both the absolute and relative treatment effects, as measured by $I^2$ values. While some of this heterogeneity may be due to real differences in patient populations between the different sites, some may be due to different amounts of bias resulting from differing opioid prescribing patterns and outcome measurement across the different sites.

Finally, the reliance on routinely collected data to generate the study samples means that there may be a susceptibility to measurement error in the exposure (e.g., patients receiving discharge prescriptions free of charge from the hospital may be misclassified as nonusers, people filling prescriptions who ultimately never took them, or issues with not being able to detect prescriptions prescribed by specialists or provided for free, both of which could only be captured in a formal validation study), covariates (e.g., not identifying older

diverticulitis or diverticulosis diagnoses or claims data lacking sensitivity for these conditions due to lack of validated definitions for these, irritable bowel syndrome, and Crohn disease as covariates), and the outcome (e.g., imperfect sensitivity and specificity, especially as these were not validated outcome definitions). Postsurgical follow-up in patients receiving bowel surgery, for example, may have resulted in elevated chances of detecting our outcomes. However, no short-term spike in incidence was observed in either phase of the study. Using a single landmark period at each site meant that we were not able to explore whether the timing of opioid initiation following surgery (which may be indicative of complications or poor recovery) was associated with poorer outcomes among new users. Finally, while missing data are often a concern, it was infrequent in the routinely collected administrative data used in this analysis.

## Conclusions and Implications for Decision or Policy-Making

**Main Take-Aways**

- Our results suggest that the rate of diverticulitis associated with the use of opioids may be low.
- Greater potential associations were observed in the trauma and other pain indication cohorts than in the postsurgical cohort.
- Although the observed risk may be low and initiation of opioids alone has minimal long-term association with diverticulitis, health care providers may need to be particularly cautious about sustained opioid use for patients who are at higher risk for diverticulitis, such as older adults.

In analyses using data from more than 20 million patients treated for pain following surgery in Alberta, British Columbia, Manitoba, Ontario, Saskatchewan, the UK CPRD, and the US Merative MarketScan, higher incidence rates, and risks of diverticulitis and severe diverticulitis were observed in patients initiating opioid use within 7 days of surgery and continuing (versus not receiving any opioids at all). After pooling estimates from across these data sources there were small but not statistically significant increases of 7.97 events per 10,000 person-years for general diverticulitis (outcome 1) and a small and statistically significant increase of 3.29 events per 10,000 person-years for hospitalized diverticulitis (outcome 2) among new users of opioids following surgery who sustained their opioid use compared to those with no exposure to opioids. While the pooled IRR of 1.38 for outcome 1 was not statistically significant, the pooled IRR of 2.34 for outcome 2 was. However, additional analyses in other indication cohorts suggested potentially stronger associations between sustained new use versus nonuse of opioids and outcome 2 in the trauma cohort (IRR = 3.96, IRD = 5.78 events per 10,000 person-years) and other pain cohorts (IRR = 4.38, IRD = 11.08 per 10,000 person-years), particularly in older patients. Moreover, the pooled 730-day RRs (1.37 for outcome 1 and 2.22 for outcome 2) in the postsurgical cohort were farther from the null than the pooled 30-day RRs (1.20 for outcome 1 and 1.38 for outcome 2), suggesting the association between opioid use and diverticulitis may increase over time.

Importantly, this association could be biased away from the null due to selection bias from associations between reasons for continuing opioid use and risk of diverticulitis, with this selection bias being differential

across cohorts. However, even if estimates are unbiased, the rarity of severe diverticulitis events in the populations we studied (7.6 per 10,000 person-years in the postsurgical population, 5.5 per 10,000 years in the trauma population, and 10.0 per 10,000 years in the other pain population) means that the absolute number of events resulting from opioid use within these patient populations is likely to be low, especially compared to other adverse events that may result from sustained opioid use. The estimated number of patients that would need to initiate opioids to cause 1 additional outcome 2 event within 30 days after the landmark (i.e., the number needed to harm) based on our results in the postsurgical group would be very high at around 100,000, while the 730-day number needed to harm would be more than 1 in 4,000 patients who initiate and use opioids continuously for that 2-year duration. That said, the IRRs of 4.0 and 4.4 in the trauma and other pain cohorts and the elevated IRDs in patients aged 65 years and older in those cohorts suggest diverticulitis may be another reason (in addition to existing well-established adverse events) for caution surrounding initiation and sustained use of opioids in older patients and education surrounding early warning signs of diverticulitis.

# References


1. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain Ther*. Jun 2018;7(1):13-21. doi:10.1007/s40122-018-0097-6 PubMed
2. Shaikh A, Khrais A, Le A, Kaye AJ, Ahlawat S. Pre-existing Opioid Use Worsens Outcomes in Patients With Diverticulitis. *Cureus*. Feb 2023;15(2):e34624. doi:10.7759/cureus.34624 PubMed
3. Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol*. May 2011;106(5):835-42; quiz 843. doi:10.1038/ajg.2011.30 PubMed
4. Gravante G, Yahia S. Medical influences, surgical outcomes: role of common medications on the risk of perforation from untreated diverticular disease. *World J Gastroenterol*. Sep 28 2013;19(36):5947-52. doi:10.3748/wjg.v19.i36.5947 PubMed
5. Humes DJ, Fleming KM, Spiller RC, West J. Concurrent drug use and the risk of perforated colonic diverticular disease: a population-based case-control study. *Gut*. Feb 2011;60(2):219-24. doi:10.1136/gut.2010.217281 PubMed
6. Piekarek K, Israelsson LA. Perforated colonic diverticular disease: the importance of NSAIDs, opioids, corticosteroids, and calcium channel blockers. *Int J Colorectal Dis*. Dec 2008;23(12):1193-7. doi:10.1007/s00384-008-0555-4 PubMed
7. Morris CR, Harvey IM, Stebbings WS, Speakman CT, Kennedy HJ, Hart AR. Anti-inflammatory drugs, analgesics and the risk of perforated colonic diverticular disease. *Br J Surg*. Oct 2003;90(10):1267-72. doi:10.1002/bjs.4221 PubMed
8. Kvasnovsky CL, Papagrigoriadis S, Bjarnason I. Increased diverticular complications with nonsteriodal anti-inflammatory drugs and other medications: a systematic review and meta-analysis. *Colorectal Dis*. Jun 2014;16(6):O189-96. doi:10.1111/codi.12516 PubMed
9. Awad AK, Varney J, Motawea KR, et al. Opioid induced colonic diverticular disease: a systematic review and meta-analysis. Paper presented at: SHM Converge 2022 Conference; April 7-10, 2022; Nashville, TN. Abstract G8. Accessed August 4, 2024. https://shmabstracts.org/abstract/opioid-induced-colonic-diverticular-disease-a-systematic-review-and-meta-analysis/
10. Suissa S, Henry D, Caetano P, et al. CNODES: the Canadian Network for Observational Drug Effect Studies. *Open Med*. 2012;6(4):e134-40. PubMed
11. Platt RW, Henry DA, Suissa S. The Canadian Network for Observational Drug Effect Studies (CNODES): Reflections on the first eight years, and a look to the future. *Pharmacoepidemiol Drug Saf*. Jan 2020;29 Suppl 1:103-107. doi:10.1002/pds.4936 PubMed
12. Pasricha SV, Tadrous M, Khuu W, et al. Clinical indications associated with opioid initiation for pain management in Ontario, Canada: a population-based cohort study. *Pain*. Aug 2018;159(8):1562-1568. doi:10.1097/j.pain.0000000000001242 PubMed
13. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol*. Dec 1 2019;48(6):1740-1740g. doi:10.1093/ije/dyz034 PubMed
14. Duchesneau ED, Jackson BE, Webster-Clark M, et al. The Timing, the Treatment, the Question: Comparison of Epidemiologic Approaches to Minimize Immortal Time Bias in Real-World Data Using a Surgical Oncology Example. *Cancer Epidemiol Biomarkers Prev*. Nov 2 2022;31(11):2079-2086. doi:10.1158/1055-9965.Epi-22-0495 PubMed
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-83. doi:10.1016/0021-9681(87)90171-8 PubMed
16. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. Jun 1992;45(6):613-9. doi:10.1016/0895-4356(92)90133-8 PubMed
17. Rassen JA, Bartels DB, Schneeweiss S, Patrick AR, Murk W. Measuring prevalence and incidence of chronic conditions in claims and electronic health record databases. *Clin Epidemiol*. 2019;11:1-15. doi:10.2147/clep.S181242 PubMed
18. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med*. Jun 2014;275(6):570-80. doi:10.1111/joim.12197 PubMed
19. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed*. Jul 2004;75(1):45-9. doi:10.1016/j.cmpb.2003.10.004 PubMed

20. Cain LE, Cole SR. Inverse probability-of-censoring weights for the correction of time-varying noncompliance in the effect of randomized highly active antiretroviral therapy on incident AIDS or death. *Stat Med*. May 30 2009;28(12):1725-38. doi:10.1002/sim.3585 PubMed

21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. Nov 10 2009;28(25):3083-107. doi:10.1002/sim.3697 PubMed

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. Sep 1986;7(3):177-88. doi:10.1016/0197-2456(86)90046-2 PubMed

# Authors and Contributors

**CNODES Disclaimer:** The opinions, results, and conclusions contained in this report are those of the authors. No endorsement by Health Canada, Canada's Drug Agency, the provinces, data stewards, the Government of Alberta, Alberta Health or Alberta Health Services, the Manitoba Centre for Health Policy or Manitoba Health, Institute for Clinical Evaluative Sciences (ICES), the participating research centres, or the Canadian Institute for Health Information (CIHI) is intended or should be inferred.

### Authors

**Michael Webster-Clark**, as the project lead, drafted the scientific protocol and statistical analysis plan; reviewed and interpreted the study results; and drafted, reviewed, and approved the report.

**Robert Platt**, as the methods lead, reviewed the scientific protocol, the statistical analysis plan, and the report.

**Greg Carney**, as the British Columbia and US Merative MarketScan site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to British Columbia and US Merative MarketScan context; oversaw submission and approval of data access and ethics approval at British Columbia and US Merative MarketScan sites; supervised British Columbia and US Merative MarketScan analyses and conducted quality checks and review of results before reporting; and reviewed and approved the report.

**Matt Dahl**, as the lead analyst and Manitoba site analyst, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Manitoba context; conducted analyses at the Manitoba site and quality checks of results; and reviewed and approved the report.

**Antonios Douros**, as the UK CPRD site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to UK CPRD context; oversaw submission and approval of data access and ethics approval at UK CPRD site; supervised UK CPRD analyses and conducted quality checks and review of results before reporting; and reviewed and approved the report.

**Christopher Filliter**, as the UK CPRD site analyst, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to UK CPRD context; conducted analyses at UK CPRD site and quality checks of results; and reviewed and approved the report.

**Amani Hamad**, as the Manitoba site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Manitoba context; oversaw submission and approval of data access and ethics approval at the Manitoba site; supervised Manitoba analyses and conducted quality checks and review of results before reporting; and reviewed and approved the report.

**Tyrone Harrison**, as the Alberta site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Alberta context; oversaw submission and approval

of data access and ethics approval at the Alberta site; supervised Alberta analyses and conducted quality checks and review of results before reporting; and reviewed and approved the report.

**Donica Janzen**, as the Saskatchewan site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Saskatchewan context; oversaw submission and approval of data access and ethics approval at the Saskatchewan site; supervised Saskatchewan analyses and conducted quality checks and review of results before reporting; and reviewed and approved the report.

**David Juurlink**, as the content expert, reviewed the scientific protocol, the statistical analysis plan, and the report.

**Jason Kim**, as the British Columbia and US Merative MarketScan site analyst, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to US Merative MarketScan and British Columbia context; conducted analyses at the US Merative MarketScan and British Columbia sites and quality checks of results; and reviewed and approved the report.

**Xinya Lu**, as the Saskatchewan site analyst, reviewed and provided feedback on the scientific protocol and the statistical analysis plan, particularly with respect to Saskatchewan context; conducted analyses at the Saskatchewan site and quality checks of results; and reviewed and approved the report.

**Carolina Moriello**, as the research assistant, contributed to drafting the scientific protocol and statistical analysis plan; contributed to review, pooling of site-specific results, and interpretation of the study results; and drafted, reviewed, and approved the report.

**J. Michael Paterson**, as the Ontario site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Ontario context; oversaw request for data access approval at the Ontario site; supervised Ontario analyses and conducted quality checks and review of results before reporting; and reviewed and approved the report.

**Audray St-Jean**, as the research assistant, contributed to review, pooling of site-specific results, and interpretation of the study results; and drafted, reviewed, and approved the report.

**Laura Targownik**, as the content expert, reviewed the scientific protocol, the statistical analysis plan, and the report.

**Fangyun Wu**, as the Ontario site analyst, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Ontario context; conducted analyses at the Ontario site and quality checks of results; and reviewed and approved the report.

**Jianguo Zhang**, as the Alberta site analyst, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Alberta context; conducted analyses at the Alberta site and quality checks of results; and reviewed and approved report.

### Contributors

**Tarita Miller**, as the US Merative MarketScan site analyst, was responsible for acquisition and analysis of data.

### Clinical Experts

This individual kindly provided comments on this report:

**Harminder Singh**, MD, MPH

Associate Professor of Medicine

University of Manitoba

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Access to data provided by the data stewards is subject to approval but can be requested for research projects through the data stewards or their designated service providers. The following British Columbia datasets were used in this study: Consolidation File (MSP Registration and Premium Billings), Medical Services Plan (MSP), Discharge Abstract Database, BC Vital Events and Statistics Deaths, National Ambulatory Care Reporting System (NACRS), and PharmaNet. You can find further information regarding these datasets by visiting the PopData project webpage at: https://my.popdata.bc.ca/project_listings/24-019/collection_approval_dates.

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CNODES is led by the CNODES steering committee and comprises many researchers who have provided significant support to this project.

## Conflicts of Interest

**Robert Platt disclosed the following:**

Since 2019, served as a consultant for 7 companies, some as a consulting expert for Analysis Group, an economics consulting company.

Payment as Advisor or Consultant

- Biogen — multiple drugs, 2017 to 2023. Advice on general methodological issues regarding multiple drugs including Tysabri and Tecfidera (multiple sclerosis) and Aduhelm (Alzheimer disease). This work terminated in December 2023.
- Boehringer Ingelheim — endowed chair 2016 to present; consultant on patient issues July 2022 to September 2022.
- Merck — vaccines (MMR, Zostavax), Singulair asthma treatment 2018 to present. Expert witness in 3 legal matters, ongoing. Advisor on study design for observational studies in reproductive medicine.
- Nant Pharma — Abraxane, 2020 to 2021. Expert in arbitration case, terminated 2021.
- Vanda Pharma — Hetlioz. Study steering committee in pediatric observational studies of latanoprost.
- Viatris (purchased from Pfizer) — latanoprost, 2014 to present. Advised on arbitration hearing.
- Finsbury — medical device. Expert reports in litigation, terminated summer 2019.

Payment for Academic Appointments (Endowed Chairs)

- Boehringer Ingelheim — endowed chair 2016 to present; consultant July 2022 to September 2022.
- Precision Analytics — serving as scientific-strategic advisor for a small consulting company developed by former students. No compensation received for this work.

**Donica Janzen disclosed the following:**

Travel Funding or Payment

- CNODES — student travel award

**David Juurlink disclosed the following:**

- Member of Physicians for Responsible Opioid Prescribing
- Member of the American College of Medical Toxicology
- Provided lectures and medicolegal opinions regarding the safety and effectiveness of analgesics, including opioids.

**Laura Targownik disclosed the following:**

Speaking Engagements

- Janssen – Remicade, Stelara
- Abbvie – Humira, Rinvoq, Skyrizi
- Takeda – Entyvio
- Pfizer – Xeljanz, inflextra
- Bristol Myers Squibb – Zeposia
- Lilly – mirikizumab
- Fresenius Kabi – Idacio

Educational Lectures

- Janssen – Remicade, Stelara
- Takeda – Entyvio
- Organon – Hadlima
- Bristol Myers Squibb – Zeposia
- Lilly – mirikizumab

Payment as Advisor or Consultant

- Janssen – Remicade, Stelera, Tremfya
- Abbvie – Humira, Rinvoq, Skyrizi
- Takeda – Entyvio
- Pfizer – Xeljanz, inflextra, etrasimod
- Organon – Hadlima
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- Viatris – Hulio
- Bristol Myers Squibb – Zeposia
- Celltrion – Yuflyma

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- Janssen – Remicade, Stelera, Tremfya
- Abbvie – Humira, Rinvoq, Skyrizi
- Takeda – Entyvio
- Pfizer – Xeljanz, inflextra, etrasimod
- Sandoz – Hyrimoz. Development of IBD Registry and for investigator-initiated research
- Amgen – Amgevita, Avsola
- Roche – etrolizumab

Member of Scientific Advisory Board

- Goodcap Pharmaceuticals

No other conflicts of interest were declared.

# Appendix 1: Additional Information on Methods

Please note that this appendix has not been copy-edited.

## Table 10: List of Diagnosis and Procedure Codes to Define the Indication Cohorts

| Indication cohort | Subclass | Diagnosis codes | Procedure codes[a] |
|---|---|---|---|
| **Postsurgical pain** | Common excision | NA | CCI codes: 1YS87, 1YF87, 1YA87, 1YB87, 1YC87, 1YD87, 1YE87, 1YG87, 1YK87, 1YM87, 1YR87, 1YS87, 1YT87, 1YU87, 1YV87, 1YW87, 1YY87, 1YZ87 |
| | Hip and knee replacement | NA | CCI codes: 1VA53, 1VG53, 1VG80 |
| | Hernia repair | NA | CCI code: 1SY80 |
| | Caesarean section | NA | CCI code: 5MD60 |
| | Other surgery[b] | NA | CCI codes: 1FR87, 1NV89, 1MD87, 1PL74, 2GM70, 1BN72, 1CL89, 1CL59, 2RN71, 1OD89, 1QD89, 1RN87, 1IJ50, 1IJ76, 1VL80, 1RM87, 1TB52, 1EY87, 1NF53, 1NT87, 1RM89, 1PE50, 1PG50, 1CH87, 1VG87, 1OT72, 1WJ80, 1DF53, 1HZ53, 1NM87D, 1NM87L, 1NM87P, 1NM87R, 1NM87T, 1NQ59DA, 1NQ59LA, 1NQ87C, 1NQ87D, 1NQ87L, 1NQ87P, 1NQ87R, 1NQ87T, 1YM87, 1RB87, 1VP80, 2RF58, 1QT91, 1YM78, 1RD89, 1RS80, 1ET80, 1TC80, 1TB80, 1KR58, 1SC75, 1FR89, 1CJ52, 1QT87, 1PG57, 1PM87, 1RF51, 1KR87, 1QN51, 1CM89 |
| **Pain after trauma** | Dislocations, sprains and strains | ICD-9-CM codes: 831, 839, 840, 842, 844, 845, 847<br>ICD-10-CA codes: S03, S13, S16, S23, S33, S43, S46, S53, S56, S63,<br>S66, S73, S76, S83, S86, S93, S96, T03 | NA |
| | Fractures and major trauma | ICD-9-CM codes: 802, 803, 805, 806, 807, 808, 810, 812, 813, 814, 815, 816, 821, 823, 824, 829<br>ICD-10-CA codes: S02, S12, S22, S28, S32, S38, S42, S47, S52, S57, S62, S67, S68, S72, S77, S82, S87, S92, S97, S98, T02, T04, T08, T10, T12 | CCI codes: 1WA74, 1VC74, 1TV74, 1VQ74, 1VA74 |
| | Burns, wounds, superficial | ICD-9-CM codes: 696, 707, 709, 879, 884, 894, 919, 949<br>ICD-10-CA codes: L10, L12, L13, L40, L57, L72, L73, L88, L89, | NA |

| Indication cohort | Subclass | Diagnosis codes | Procedure codes[a] |
|---|---|---|---|
| | | L94, L95, L97, L98, S01, S11, S21, S31, S41, S51, S61, S71, S81, S91, T01, T20, T21, T22, T23, T24, T25, T26, T28, T29, T30, T31, T33, T35, Z43 | |
| | Other trauma | ICD-9-CM codes: 767, 854, 869, 930, 959<br>ICD-10-CA codes: O71, S04, S05, S06, S09, S14, S19, S24, S26, S27, S29, S34, S35, S36, S37, S39, S44, S49, S54, S55, S59, S64, S65, S69, S74, S75, S79, S89, S99, T06, T07, T09, T11, T13, T14, T15, T16, T17, T18, T19, T74, T79 | NA |
| **Other indications for opioids** | Nephrolithiasis and cholecystitis | ICD-9-CM code: 592<br>ICD-10-CA code: N20 | CCI codes: 1PE59, 1PG59, 1PM59 |
| | Nonsurgical deliveries | NA | CCI codes: 5MD50, 5MD23, 5MD54, 5MD55, 5MD56, 5PC80 |
| | Headache and migraine | ICD-9-CM codes: 346, 780<br>ICD-10-CA codes: G43, G44, R51 | NA |
| | Back pain | ICD-10-CA code: M54 | NA |

CCI = Canadian Classification of Health Interventions; ICD-9-CM = International Classification of Diseases, Ninth Revision; ICD-10-CA = International Classification of Diseases, 10th revision with Canadian enhancement; NA = not applicable.

[a]Other site-specific procedure codes used as applicable.

[b]Source for other surgery codes: Feinberg et al. Regional variation in the use of surgery in Ontario. *CMAJ Open*. 2015. DOI:10.9778/cmajo.20150014.

## Table 11: List of Databases Used in Each Participating Site

| CNODES site | Database | | | | |
|---|---|---|---|---|---|
| | Prescription drug claims (dispensing captured) | Physician service claims | Hospital records | Emergency department records | Health insurance registry |
| **Alberta** | Pharmaceutical Information Network (all) | Practitioner Claims | CIHI Discharge Abstract Database | NACRS | Provincial Registry |
| **British Columbia** | British Columbia PharmaNet (all)[a] | British Columbia Medical Services Plan | CIHI Discharge Abstract Database | NACRS | British Columbia Ministry of Health Client Roster |
| **Manitoba** | Drug Program Information Network (all) | Medical Claims/ Medical Services | CIHI Discharge Abstract/ Manitoba Hospital Abstracts | Not available | Manitoba Health Insurance Registry |

| CNODES site | Database | | | | |
|---|---|---|---|---|---|
| | Prescription drug claims (dispensing captured) | Physician service claims | Hospital records | Emergency department records | Health insurance registry |
| **Ontario** | Narcotics Monitoring System (all monitored drugs) | OHIP Claims History Database | CIHI Discharge Abstract Database | NACRS | OHIP Registered Persons Database |
| **Saskatchewan** | Prescription Drug Plan Historical Claims (all) | Medical Services Branch | CIHI Discharge Abstract Database | NACRS | Person Health Registration System |
| **UK CPRD** | Drug issue (prescriptions) | Consultation/ observation/referral/ problem | HES Admitted Patient Care | Not available | Aurum |
| **US Merative MarketScan**[b] | Outpatient prescription drug claims (all) | Outpatient services | Inpatient admissions and inpatient services | Outpatient services (where place of service is emergency department) | Enrolment |

CIHI = Canadian Institute for Health Information; CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics; NACRS = National Ambulatory Care Reporting System; OHIP = Ontario Health Insurance Plan.

[a]Excludes patients who are federally insured and beneficiaries of the First Nations Health Benefits plan.

[b]The US Merative MarketScan Research Databases includes the Commercial Claims and Encounters database and Supplemental and Coordination of Benefits (COB) database.

## Table 12: Start and End Dates of Data Availability in Each Participating Site

| CNODES site | Start date of data availability | End date of data availability |
|---|---|---|
| **Alberta** | January 1, 2008 | March 31, 2020 |
| **British Columbia** | April 1, 2004 | March 31, 2020 |
| **Manitoba** | April 1, 2004 | March 31, 2020 |
| **Ontario** | July 1, 2012 | March 31, 2020 |
| **Saskatchewan** | April 1, 2004 | March 31, 2020 |
| **UK CPRD** | April 1, 2004 | March 31, 2020 |
| **US Merative MarketScan** | January 1, 2006 | March 31, 2020 |

CPRD = Clinical Practice Research Datalink.

Note: For Saskatchewan the nonadjudicated drug claims were available from April 1, 2008, onward and NACRS from April 1, 2012, onward.

## Table 13: List of ATC Codes to Define Opioids Exposure

| Medication | ATC codes |
|---|---|
| **Opioids** | A07DA02 opium<br>A07DA52 morphine, combinations<br>M03BA53 methocarbamol, combinations excl. psycholeptics |

| Medication | ATC codes |
|---|---|
| | N01AH01 fentanyl<br>N01AH02 alfentanil<br>N01AH03 sufentanil<br>N01AH05 anileridine<br>N01AH06 remifentanil<br>N01AH51 fentanyl, combinations<br>N02AA01 morphine<br>N02AA02 opium<br>N02AA03 hydromorphone<br>N02AA05 oxycodone<br>N02AA11 oxymorphone<br>N02AA51 morphine, combinations<br>N02AA53 hydromorphone and naloxone<br>N02AA55 oxycodone and naloxone<br>N02AA56 oxycodone and naltrexone<br>N02AA58 dihydrocodeine, combinations<br>N02AA59 codeine, combinations excl. psycholeptics<br>N02AA79 codeine, combinations with psycholeptics<br>N02AB02 pethidine<br>N02AB03 fentanyl<br>N02AC04 dextropropoxyphene<br>N02AC54 dextropropoxyphene, combinations excl. psycholeptics<br>N02AD01 pentazocine<br>N02AE01 buprenorphine<br>N02AF01 butorphanol<br>N02AF02 nalbuphine<br>N02AG01 morphine and antispasmodics<br>N02AG04 hydromorphone and antispasmodics<br>N02AJ01 dihydrocodeine and paracetamol<br>N02AJ02 dihydrocodeine and AAS<br>N02AJ03 dihydrocodeine and other nonopioids analgesics<br>N02AJ06 codeine and paracetamol<br>N02AJ07 codeine and AAS<br>N02AJ08 codeine and ibuprofen<br>N02AJ09 codeine and other nonopioids analgesics<br>N02AJ13 tramadol and paracetamol<br>N02AJ14 tramadol and AAS<br>N02AJ15 tramadol and ibuprofen<br>N02AJ16 tramadol and celecoxib<br>N02AJ17 oxycodone and paracetamol<br>N02AJ18 oxycodone and AAS<br>N02AJ19 oxycodone and ibuprofen<br>N02AX02 tramadol |

| Medication | ATC codes |
|---|---|
| | N02AX06 tapentadol<br>N02BA51 AAS, combinations excl. psycholeptics<br>N02BA71 AAS, combinations with psycholeptics<br>N02BE01 paracetamol<br>N02BE51 paracetamol, combinations excl. psycholeptics<br>N07BC02 methadone<br>N07BC06 diamorphine<br>N07BC51 buprenorphine, combinations<br>R05DA03 hydrocodone<br>R05DA04 codeine<br>R05DA20 combinations (opium alkaloids and derivates)<br>R05FA02 opium derivatives and expectorants<br>R05FB02 cough suppressants and expectorants |

ATC = anatomic therapeutic chemical.

## Table 14: List of Diagnosis and Procedure Codes to Define Diverticulitis Outcome

| Outcome | Diagnosis codes | Procedure codes[a] |
|---|---|---|
| **Diverticulitis** | **ICD-9-CM codes:** 562.01, 562.03, 562.11, 562.13<br>**ICD-10-CA codes:** K57.x | **CCI codes for CT scan:** 3NM20VA, 3NM20WA, 3NM20WC, 3NM20WE<br>**CCI codes for MRI:** 3OT40VA, 3OT40WA, 3OT40WC, 3OT40WE<br>**CCI codes for large bowel excision:** 1NM87DA, 1NM87DE, 1NM87DF, 1NM87DN, 1NM87DX, 1NM87DY, 1NM87GB, 1NM87LA, 1NM87PN, 1NM87RD, 1NM87RE, 1NM87RN, 1NM87TF, 1NM87TG, 1NM87WJ, 1NM89DF, 1NM89DX, 1NM89GB, 1NM89RN, 1NM89TF, 1NM89WJ, 1NM91DE, 1NM91DF, 1NM91DN 1NM91DX, 1NM91DY, 1NM91RD, 1NM91RE, 1NM91RN, 1NM91TF, 1NM91TG<br>**CCI codes for drainage:** 1NM52CA, 1NM52CATS, 1NM52DA, 1NM52HATS, 1NM52LA, 1NM52LATS, 1NM52UW<br>**CCI codes for bypass:** 1NM76DF, 1NM76DN, 1NM76RE, 1NM76RN |

CCI = Canadian Classification of Health Interventions; ICD-9-CM = International Classification of Diseases, Ninth Revision; ICD-10-CA = International Classification of Diseases, 10th revision with Canadian enhancement.

[a]Other site-specific procedure codes used as applicable.

# Appendix 2: Site-Specific Findings for Feasibility Study

Please note that this appendix has not been copy-edited.

## Table 15: Baseline Characteristics of the Feasibility Study Postsurgical Indication Cohort, by Site

| Characteristic | Alberta[a] N (%) N = 660,829 | Manitoba N (%) N = 438,191 | Ontario[b] N (%) N = 1,584,328 | Saskatchewan N (%) N = 501,812 | US Merative MarketScan N (%) N = 29,693,068 |
|---|---|---|---|---|---|
| **Nonusers** | 583,269 (88.3) | 243,481 (55.6) | 832,058 (52.5) | 364,855 (72.7) | 22,846,334 (76.9) |
| **New users** | 35,533 (5.4) | 164,607 (37.6) | 637,848 (40.3) | 113,985 (22.7) | 5,037,562 (17.0) |
| **Prevalent users** | 42,027 (6.4) | 30,103 (6.9) | 114,422 (7.2) | 22,972 (4.6) | 1,809,172 (6.1) |
| **Calendar year of study cohort entry** | | | | | |
| 2004 to 2007 | — | 134,157 (30.6) | — | 143,821 (28.7) | 4,295,728 (14.5) |
| 2008 to 2011 | 239,560 (36.3) | 115,416 (26.3) | — | 125,951 (25.1) | 11,308,997 (38.1) |
| 2012 to 2015 | 214,842 (32.5) | 96,715 (22.1) | 610,625 (38.5) | 117,987 (23.5) | 8,178,927 (27.5) |
| 2016 to 2020 | 206,427 (31.2) | 91,903 (21.0) | 973,703 (61.5) | 114,053 (22.7) | 5,909,416 (19.9) |
| **Age (years)** | | | | | |
| 18 to 39 | 219,189 (33.2) | 117,257 (26.8) | 428,409 (27.0) | 140,736 (28.0) | 8,823,232 (29.7) |
| 40 to 64 | 257,260 (38.9) | 184,432 (42.1) | 675,312 (42.6) | 189,185 (37.7) | 16,633,058 (56.0) |
| 65 to 79 | 135,691 (20.5) | 99,274 (22.7) | 388,333 (24.5) | 123,795 (24.7) | 3,175,660 (10.7) |
| 80+ | 48,689 (7.4) | 37,228 (8.5) | 92,274 (5.8) | 48,096 (9.6) | 1,061,118 (3.6) |
| **Sex** | | | | | |
| Males | 252,118 (38.2) | 177,222 (40.4) | 692,787 (43.7) | 211,491 (42.1) | 10,933,602 (36.8) |
| Females | 408,711 (61.8) | 260,969 (59.6) | 891,541 (56.3) | 290,321 (57.9) | 18,759,466 (63.2) |
| **Income quintile[c,d]** | | | | | |
| First (lowest) | 148,293 (22.4) | 84,295 (19.2) | 310,626 (19.7) | 46,090 (9.2) | — |
| Second | 144,569 (21.9) | 90,061 (20.6) | 316,538 (20.0) | 48,012 (9.6) | — |
| Third | 131,263 (19.9) | 91,400 (20.9) | 318,849 (20.2) | 46,751 (9.3) | — |
| Fourth | 119,149 (18.0) | 86,775 (19.8) | 316,773 (20.0) | 45,793 (9.1) | — |
| Fifth (highest) | 114,546 (17.3) | 82,385 (18.8) | 317,336 (20.1) | 43,550 (8.7) | — |
| **Comorbidities** | | | | | |
| History of irritable bowel syndrome | 5,858 (0.9) | 792 (0.2) | 38,726 (2.4) | 998 (0.2) | 284,070 (1.0) |
| History of Crohn disease | 6,753 (1.0) | 2,076 (0.5) | 8,279 (0.5) | 2,738 (0.6) | 98,171 (0.3) |

| Characteristic | Alberta[a] N (%) N = 660,829 | Manitoba N (%) N = 438,191 | Ontario[b] N (%) N = 1,584,328 | Saskatchewan N (%) N = 501,812 | US Merative MarketScan N (%) N = 29,693,068 |
|---|---|---|---|---|---|
| History of diverticulitis or diverticulosis | 17,984 (2.7) | 10,755 (2.5) | 33,216 (2.1) | 15,582 (3.1) | 306,774 (1.0) |
| History of myocardial infarction | 44,105 (6.7) | 18,136 (4.1) | 126,458 (8.0) | 18,231 (3.6) | 148,090 (0.5) |
| History of congestive heart failure | 32,188 (4.9) | 14,641 (3.3) | 39,953 (2.5) | 16,726 (3.3) | 252,288 (0.9) |
| Peripheral vascular disease | 15,169 (2.3) | 8,370 (1.9) | 16,147 (1.0) | 6,754 (1.4) | 259,854 (0.9) |
| Cerebrovascular accident | 18,944 (2.9) | 9,181 (2.1) | 30,775 (1.9) | 9,175 (1.8) | 426,283 (1.4) |
| Transient ischemic attack | 4,859 (0.7) | 3,022 (0.7) | 2,512 (0.2) | 2,497 (0.5) | 78,976 (0.3) |
| Dementia | 15,332 (2.3) | 5,837 (1.3) | 27,149 (1.7) | 3,457 (0.7) | 35,075 (0.1) |
| Chronic obstructive pulmonary disease | 48,009 (7.3) | 30,049 (6.9) | 59,846 (3.8) | 35,309 (7.0) | 950,295 (3.2) |
| Peptic ulcer disease | 9,572 (1.4) | 4,498 (1.0) | 13,444 (0.8) | 6,406 (1.3) | 95,832 (0.3) |
| Liver disease | 6,478 (1.0) | 3,290 (0.8) | 7,948 (0.5) | 1,950 (0.4) | 226,693 (0.8) |
| Diabetes mellitus | 92,240 (14.0) | 61,684 (14.1) | 245,200 (15.5) | 65,537 (13.1) | 2,774,126 (9.3) |
| Hemiplegia | 2,846 (0.4) | 973 (0.2) | 2,024 (0.1) | 835 (0.2) | 10,755 (0.0) |
| Chronic kidney disease | 24,065 (3.6) | 8,007 (1.8) | 38,186 (2.4) | 7,382 (1.5) | 343,853 (1.2) |
| Current tumour | 92,650 (14.0) | 45,487 (10.4) | 206,586 (13.0) | 40,957 (8.2) | 1,503,969 (5.1) |
| **Subclass of indication[e]** | | | | | |
| Common excision | 46,315 (7.0) | 21,973 (5.0) | 104,901 (6.6) | 12,895 (2.6) | 5,706,002 (19.2) |
| Knee, hip, or shoulder surgery | 83,703 (12.7) | 44,043 (10.1) | 142,163 (9.0) | 58,588 (11.7) | 505,039 (1.7) |
| Hernia repair | 24,199 (3.7) | 35,964 (8.2) | 134,794 (8.5) | 41,886 (8.4) | 45,122 (0.2) |
| Caesarean section | 114,052 (17.3) | 33,920 (7.7) | 132,783 (8.4) | 31,585 (6.3) | 1,586,454 (5.3) |
| Other surgery | 392,560 (59.4) | 325,996 (74.4) | 1,132,523 (71.5) | 356,858 (71.1) | 22,245,433 (74.9) |

Note: Postsurgical indication: 7-day landmark and 90-day lookback period.

[a]Alberta data were available as of 2008.

[b]Ontario data were available as of 2012.

[c]Missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

[d]Data were not available in US Merative MarketScan.

[e]Patients could be included in more than 1 subclass within the indication cohort.

## Table 16: Baseline Characteristics of the Feasibility Study Trauma Indication Cohort, by Site

| Characteristic | Alberta[a] N (%) N = 2,537,751 | Manitoba N (%) N = 706,491 | Ontario[b] N (%) N = 1,927,461 | Saskatchewan N (%) N = 681,017 | US Merative MarketScan N (%) N = 41,334,452 |
|---|---|---|---|---|---|
| **Nonusers** | 2,292,067 (90.3) | 607,694 (86.0) | 1,759,321 (91.3) | 613,938 (90.2) | 34,603,324 (83.7) |
| **New users** | 141,678 (5.6) | 60,327 (8.5) | 128,175 (6.6) | 48,918 (7.2) | 4,775,529 (11.6) |
| **Prevalent users** | 104,006 (4.1) | 38,470 (5.4) | 39,965 (2.1) | 18,161 (2.7) | 1,955,599 (4.7) |
| **Calendar year of study cohort entry** | | | | | |
| 2004 to 2007 | — | 277,473 (39.3) | — | 270,441 (39.7) | 5,029,974 (12.2) |
| 2008 to 2011 | 1,281,629 (50.5) | 178,214 (25.2) | — | 159,669 (23.4) | 14,094,051 (34.1) |
| 2012 to 2015 | 730,864 (28.8) | 135,445 (19.2) | 811,422 (42.1) | 134,344 (19.7) | 11,689,689 (28.3) |
| 2016 to 2020 | 525,258 (20.7) | 115,359 (16.3) | 1,116,039 (57.9) | 116,563 (17.1) | 10,520,738 (25.5) |
| **Age (years)** | | | | | |
| 18 to 39 | 1,115,222 (43.9) | 260,776 (36.9) | 784,024 (40.7) | 266,755 (39.2) | 15,264,640 (36.9) |
| 40 to 64 | 1,039,089 (40.9) | 298,437 (42.2) | 792,266 (41.1) | 274,595 (40.3) | 21,604,460 (52.3) |
| 65 to 79 | 270,075 (10.6) | 95,273 (13.5) | 259,724 (13.5) | 91,029 (13.4) | 3,071,267 (7.4) |
| 80+ | 113,365 (4.5) | 52,005 (7.4) | 91,447 (4.7) | 48,638 (7.1) | 1,394,085 (3.4) |
| **Sex** | | | | | |
| Males | 1,273,737 (50.2) | 338,783 (48.0) | 907,100 (47.1) | 334,297 (49.1) | 18,776,629 (45.4) |
| Females | 1,264,014 (49.8) | 367,708 (52.0) | 1,020,361 (52.9) | 346,720 (50.9) | 22,557,823 (54.6) |
| **Income quintile[c,d]** | | | | | |
| First (lowest) | 587,147 (23.1) | 141,233 (20.0) | 425,317 (22.1) | 105,202 (15.5) | — |
| Second | 556,840 (21.9) | 142,834 (20.2) | 396,716 (20.6) | 101,105 (14.9) | — |
| Third | 489,946 (19.3) | 142,065 (20.1) | 380,643 (19.8) | 98,449 (14.5) | — |
| Fourth | 442,906 (17.5) | 137,079 (19.4) | 365,493 (19.0) | 96,815 (14.2) | — |
| Fifth (highest) | 445,816 (17.6) | 134,963 (19.1) | 353,234 (18.4) | 92,312 (13.6) | — |
| **Comorbidities** | | | | | |
| History of irritable bowel syndrome | 13,472 (0.5) | 875 (0.1) | 27,799 (1.4) | 927 (0.1) | 401,009 (1.0) |
| History of Crohn disease | 10,011 (0.4) | 2,141 (0.3) | 5,095 (0.3) | 2,524 (0.4) | 127,326 (0.3) |
| History of diverticulitis or diverticulosis | 16,806 (0.7) | 8,253 (1.2) | 14,934 (0.8) | 9,491 (1.4) | 373,996 (0.9) |
| History of myocardial infarction | 13,615 (0.5) | 4,109 (0.6) | 45,527 (2.4) | 4,029 (0.6) | 112,754 (0.3) |

| Characteristic | Alberta[a] N (%) N = 2,537,751 | Manitoba N (%) N = 706,491 | Ontario[b] N (%) N = 1,927,461 | Saskatchewan N (%) N = 681,017 | US Merative MarketScan N (%) N = 41,334,452 |
|---|---|---|---|---|---|
| History of congestive heart failure | 34,219 (1.3) | 15,532 (2.2) | 21,525 (1.1) | 13,879 (2.0) | 508,102 (1.2) |
| Peripheral vascular disease | 20,371 (0.8) | 8,990 (1.3) | 9,235 (0.5) | 5,093 (0.8) | 494,776 (1.2) |
| Cerebrovascular accident | 28,327 (1.1) | 11,166 (1.6) | 21,392 (1.1) | 8,968 (1.3) | 799,444 (1.9) |
| Transient ischemic attack | 8,726 (0.3) | 3,610 (0.5) | 1,662 (0.1) | 2,453 (0.4) | 181,863 (0.4) |
| Dementia | 33,489 (1.3) | 12,348 (1.7) | 26,711 (1.4) | 4,595 (0.7) | 125,078 (0.3) |
| Chronic obstructive pulmonary disease | 82,211 (3.2) | 41,835 (5.9) | 34,175 (1.8) | 36,754 (5.4) | 1,475,395 (3.6) |
| Peptic ulcer disease | 14,988 (0.6) | 4,862 (0.7) | 8,117 (0.4) | 5,557 (0.8) | 140,173 (0.3) |
| Liver disease | 10,108 (0.4) | 3,511 (0.5) | 4,659 (0.2) | 2,069 (0.3) | 279,618 (0.7) |
| Diabetes mellitus | 176,586 (7.0) | 62,224 (8.8) | 171,370 (8.9) | 51,989 (7.6) | 3,502,997 (8.5) |
| Hemiplegia | 3,446 (0.1) | 1,088 (0.2) | 1,173 (0.1) | 844 (0.1) | 36,689 (0.1) |
| Chronic kidney disease | 28,589 (1.1) | 7,342 (1.0) | 25,356 (1.3) | 5,030 (0.7) | 624,354 (1.5) |
| Current tumour | 82,853 (3.3) | 28,055 (4.0) | 92,150 (4.8) | 20,192 (3.0) | 1,509,296 (3.7) |
| **Subclass of indication[e]** | | | | | |
| Dislocations, sprains, and strains | 1,138,022 (44.8) | 257,897 (36.5) | 781,630 (40.6) | 331,869 (35.8) | 16,538,904 (40.0) |
| Fracture and major trauma | 289,220 (11.4) | 97,484 (13.8) | 182,783 (9.5) | 132,209 (14.3) | 1,665,984 (4.0) |
| Burns and wounds | 784,609 (30.9) | 226,405 (32.0) | 743,147 (38.6) | 358,317 (38.7) | 14,862,828 (36.0) |
| Other trauma | 325,900 (12.8) | 132,885 (18.8) | 241,709 (12.5) | 103,709 (11.2) | 8,689,059 (21.0) |

Note: Trauma indication: 30-day landmark and 90-day lookback period.

[a]Alberta data were available as of 2008.

[b]Ontario data were available as of 2012.

[c]Missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

[d]Data were not available in US Merative MarketScan

[e]Patients could be included in more than one subclass within the indication cohort.

## Table 17: Baseline Characteristics of the Feasibility Study Dental Indication Cohort, by Site

| Characteristic | Alberta[a] N (%) N = 6,106 | Manitoba N (%) N = 9,262 | Ontario[b] N (%) N = 52,010 | Saskatchewan N (%) N = 4,998 | US Merative MarketScan N (%) N = 200,593 |
|---|---|---|---|---|---|
| **Nonusers** | 5,197 (85.1) | 2,845 (30.7) | 17,088 (32.9) | 3,149 (63.0) | 126,993 (63.3) |
| **New users** | 334 (5.5) | 4,816 (52.0) | 25,243 (48.5) | 1,422 (28.5) | 53,414 (26.6) |
| **Prevalent users** | 575 (9.4) | 1,601 (17.3) | 9,679 (18.6) | 427 (8.5) | 20,186 (10.1) |
| **Calendar year of study cohort entry** | | | | | |
| 2004 to 2007 | — | 2,468 (26.6) | — | 1,464 (29.3) | 31,983 (15.9) |
| 2008 to 2011 | 2,026 (33.2) | 2,483 (26.8) | — | 1,315 (26.3) | 76,491 (38.1) |
| 2012 to 2015 | 2,023 (33.1) | 2,326 (25.1) | 20,353 (39.1) | 1,109 (22.2) | 50,013 (24.9) |
| 2016 to 2020 | 2,057 (33.7) | 1,985 (21.4) | 31,657 (60.9) | 1,110 (22.2) | 42,106 (21.0) |
| **Age (years)** | | | | | |
| 18 to 39 | 2,429 (39.8) | 4,508 (48.7) | 21,202 (40.8) | 2,573 (51.5) | 105,199 (52.4) |
| 40 to 64 | 2,382 (39.0) | 3,304 (35.7) | 17,640 (33.9) | 1,757 (35.2) | 83,614 (41.7) |
| 65 to 79 | 788 (12.9) | 1,005 (10.9) | 8,655 (16.6) | 448 (9.0) | 9,289 (4.6) |
| 80+ | 507 (8.3) | 445 (4.8) | 4,513 (8.7) | 220 (4.4) | 2,491 (1.2) |
| **Sex** | | | | | |
| Males | 3,850 (63.1) | 5,189 (56.0) | 26,887 (51.7) | 2,615 (52.3) | 97,130 (48.4) |
| Females | 2,256 (36.9) | 4,073 (44.0) | 25,123 (48.3) | 2,383 (47.7) | 103,463 (51.6) |
| **Income quintile[c,d]** | | | | | |
| First (lowest) | 1,905 (31.2) | 2,236 (24.1) | 14,098 (27.2) | 374 (7.5) | — |
| Second | 1,366 (22.4) | 1,889 (20.4) | 11,316 (21.9) | 343 (6.9) | — |
| Third | 1,115 (18.3) | 1,689 (18.2) | 9,712 (18.8) | 304 (6.1) | — |
| Fourth | 869 (14.2) | 1,536 (16.6) | 8,498 (16.4) | 327 (6.5) | — |
| Fifth (highest) | 788 (12.9) | 1,416 (15.3) | 8,148 (15.7) | 287 (5.7) | — |
| **Comorbidities** | | | | | |
| History of irritable bowel syndrome | 39 (0.6) | 15 (0.2) | 1,448 (2.8) | S | 2,023 (1.0) |
| History of Crohn disease | 52 (0.9) | 33 (0.4) | 311 (0.6) | 22 (0.4) | 678 (0.3) |
| History of diverticulitis or diverticulosis | 60 (1.0) | 85 (0.9) | 655 (1.3) | 36 (0.7) | 1,434 (0.7) |
| History of myocardial infarction | 316 (5.2) | 104 (1.1) | 4,156 (8.0) | 43 (0.9) | 619 (0.3) |
| History of congestive heart failure | 685 (11.2) | 353 (3.8) | 2,338 (4.5) | 117 (2.3) | 2,540 (1.3) |

| Characteristic | Alberta[a] N (%) N = 6,106 | Manitoba N (%) N = 9,262 | Ontario[b] N (%) N = 52,010 | Saskatchewan N (%) N = 4,998 | US Merative MarketScan N (%) N = 200,593 |
|---|---|---|---|---|---|
| Peripheral vascular disease | 255 (4.2) | 168 (1.8) | 825 (1.6) | 42 (0.8) | 2,122 (1.1) |
| Cerebrovascular accident | 413 (6.8) | 259 (2.8) | 1,993 (3.8) | 105 (2.1) | 4,045 (2.0) |
| Transient ischemic attack | 73 (1.2) | 59 (0.6) | 123 (0.2) | 11 (0.2) | 804 (0.4) |
| Dementia | 474 (7.8) | 234 (2.5) | 2,950 (5.7) | 73 (1.5) | 535 (0.3) |
| Chronic obstructive pulmonary disease | 757 (12.4) | 628 (6.8) | 4,109 (7.9) | 317 (6.3) | 7,422 (3.7) |
| Peptic ulcer disease | 98 (1.6) | 77 (0.8) | 564 (1.1) | 61 (1.2) | 654 (0.3) |
| Liver disease | 168 (2.8) | 100 (1.1) | 647 (1.2) | 41 (0.8) | 1,539 (0.8) |
| Diabetes mellitus | 1,030 (16.9) | 1,265 (13.7) | 9,241 (17.8) | 421 (8.4) | 15,176 (7.6) |
| Hemiplegia | 103 (1.7) | 43 (0.5) | 141 (0.3) | 11 (0.2) | 311 (0.2) |
| Chronic kidney disease | 406 (6.6) | 185 (2.0) | 1,945 (3.7) | 61 (1.2) | 2,761 (1.4) |
| Current tumour | 754 (12.3) | 627 (6.8) | 4,885 (9.4) | 204 (4.1) | 10,245 (5.1) |

S = suppressed value.

Notes: Dental indication: 7-day landmark and 90-day lookback period.

Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a]Alberta data were available as of 2008.

[b]Ontario data were available as of 2012.

[c]Missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

[d]Data were not available in US Merative MarketScan.

## Table 18: Baseline Characteristics of the Feasibility Study Other Pain Indication Cohort, by Site

| Characteristic | Alberta[a] N (%) N = 2,890,117 | Manitoba N (%) N = 642,762 | Ontario[b] N (%) N = 1,816,978 | Saskatchewan N (%) N = 627,082 | US Merative MarketScan N (%) N = 50,598,794 |
|---|---|---|---|---|---|
| **Nonusers** | 2,695,818 (93.3) | 586,476 (91.2) | 1,579,800 (86.9) | 581,650 (92.8) | 43,972,255 (86.9) |
| **New users** | 100,865 (3.5) | 25,554 (4.0) | 163,618 (9.0) | 25,476 (4.1) | 4,540,407 (9.0) |
| **Prevalent users** | 93,434 (3.2) | 30,732 (4.8) | 73,560 (4.1) | 19,956 (3.2) | 2,086,132 (4.1) |
| **Calendar year of study cohort entry** | | | | | |
| 2004 to 2007 | — | 223,103 (34.7) | — | 200,338 (31.9) | 6,811,593 (13.5) |
| 2008 to 2011 | 1,464,446 (50.7) | 150,256 (23.4) | — | 139,516 (22.2) | 18,549,000 (36.7) |
| 2012 to 2015 | 826,639 (28.6) | 129,774 (20.2) | 718,161 (39.5) | 138,158 (22.0) | 14,543,467 (28.7) |
| 2016 to 2020 | 599,032 (20.7) | 139,629 (21.7) | 1,098,817 (60.5) | 149,070 (23.8) | 10,694,734 (21.1) |
| **Age (years)** | | | | | |

| Characteristic | Alberta[a] N (%) N = 2,890,117 | Manitoba N (%) N = 642,762 | Ontario[b] N (%) N = 1,816,978 | Saskatchewan N (%) N = 627,082 | US Merative MarketScan N (%) N = 50,598,794 |
|---|---|---|---|---|---|
| 18 to 39 | 1,317,751 (45.6) | 268,602 (41.8) | 762,050 (41.9) | 264,416 (42.2) | 20,313,293 (40.2) |
| 40 to 64 | 1,131,216 (39.1) | 244,866 (38.1) | 675,586 (37.2) | 225,224 (35.9) | 25,234,153 (49.9) |
| 65 to 79 | 315,888 (10.9) | 85,355 (13.3) | 277,283 (15.3) | 86,186 (13.7) | 3,465,046 (6.9) |
| 80+ | 125,262 (4.3) | 43,939 (6.8) | 102,059 (5.6) | 51,256 (8.2) | 1,586,302 (3.1) |
| **Sex** | | | | | |
| Males | 1,330,716 (46.0) | 253,718 (39.5) | 796,400 (43.8) | 265,174 (42.3) | 19,329,268 (38.2) |
| Females | 1,559,401 (54.0) | 389,044 (60.5) | 1,020,578 (56.2) | 361,908 (57.7) | 31,269,526 (61.8) |
| **Income quintile[c,d]** | | | | | |
| First (lowest) | 694,655 (24.0) | 132,214 (20.6) | 389,670 (21.5) | 62,174 (9.9) | — |
| Second | 638,537 (22.1) | 127,400 (19.8) | 371,933 (20.5) | 59,380 (9.5) | — |
| Third | 552,659 (19.1) | 128,801 (20.0) | 363,780 (20.1) | 55,300 (8.8) | — |
| Fourth | 496,107 (17.2) | 124,781 (19.4) | 350,794 (19.4) | 53,151 (8.5) | — |
| Fifth (highest) | 492,152 (17.0) | 122,838 (19.1) | 335,146 (18.5) | 49,837 (8.0) | — |
| **Comorbidities** | | | | | |
| History of irritable bowel syndrome | 14,706 (0.5) | 834 (0.1) | 34,969 (1.9) | 936 (0.2) | 428,009 (0.9) |
| History of Crohn disease | 10,727 (0.4) | 1,981 (0.3) | 6,035 (0.3) | 2,516 (0.4) | 143,764 (0.3) |
| History of diverticulitis or diverticulosis | 18,935 (0.7) | 7,470 (1.2) | 19,630 (1.1) | 9,679 (1.5) | 349,144 (0.7) |
| History of myocardial infarction | 20,200 (0.7) | 4,008 (0.6) | 56,824 (3.1) | 6,442 (1.0) | 147,479 (0.3) |
| History of congestive heart failure | 39,773 (1.4) | 12,565 (2.0) | 26,257 (1.4) | 17,128 (2.7) | 579,105 (1.1) |
| Peripheral vascular disease | 22,757 (0.8) | 7,033 (1.1) | 11,986 (0.7) | 5,750 (0.9) | 532,117 (1.1) |
| Cerebrovascular accident | 35,506 (1.2) | 10,812 (1.7) | 41,785 (2.3) | 13,485 (2.2) | 817,112 (1.6) |
| Transient ischemic attack | 13,731 (0.5) | 4,572 (0.7) | 5,307 (0.3) | 4,523 (0.7) | 183,279 (0.4) |
| Dementia | 34,704 (1.2) | 8,102 (1.3) | 28,225 (1.6) | 5,188 (0.8) | 99,409 (0.2) |
| Chronic obstructive pulmonary disease | 92,660 (3.2) | 37,916 (5.9) | 43,200 (2.4) | 37,162 (5.9) | 1,680,857 (3.3) |
| Peptic ulcer disease | 18,118 (0.6) | 4,349 (0.7) | 9,870 (0.5) | 6,130 (1.0) | 153,565 (0.3) |

| Characteristic | Alberta[a] N (%) N = 2,890,117 | Manitoba N (%) N = 642,762 | Ontario[b] N (%) N = 1,816,978 | Saskatchewan N (%) N = 627,082 | US Merative MarketScan N (%) N = 50,598,794 |
|---|---|---|---|---|---|
| Liver disease | 11,772 (0.4) | 3,289 (0.5) | 5,775 (0.3) | 2,508 (0.4) | 327,011 (0.7) |
| Diabetes mellitus | 193,681 (6.7) | 52,144 (8.1) | 190,515 (10.5) | 53,830 (8.6) | 3,963,266 (7.8) |
| Hemiplegia | 4,466 (0.2) | 801 (0.1) | 1,639 (0.1) | 1,288 (0.2) | 34,681 (0.1) |
| Chronic kidney disease | 30,231 (1.0) | 5,388 (0.8) | 30,566 (1.7) | 6,716 (1.1) | 645,403 (1.3) |
| Current tumour | 98,075 (3.4) | 25,934 (4.0) | 110,292 (6.1) | 24,237 (3.9) | 1,702,319 (3.4) |
| **Subclass of indication[e]** | | | | | |
| Nephrolithiasis or cholecystitis | 57,929 (2.0) | 26,130 (4.1) | 124,329 (6.8) | 19,910 (2.5) | 1,663,360 (3.3) |
| Headache and migraine | 2,569,035 (88.9) | 535,398 (83.3) | 1,209,417 (66.6) | 684,578 (86.5) | 37,969,521 (75.0) |
| Nonsurgical deliveries | 137,255 (4.8) | 75,881 (11.8) | 200,448 (11.0) | 67,031 (8.5) | 3,949,463 (7.8) |
| Back pain | 125,898 (4.4) | 5,478 (0.9) | 284,691 (15.7) | 19,764 (2.5) | 7,318,122 (14.5) |

Note: Other pain indication: 30-day landmark and 90-day lookback.

[a]Alberta data were available as of 2008.

[b]Ontario data were available as of 2012.

[c]Missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

[d]Data were not available in US Merative MarketScan.

[e]Patients could be included in more than 1 subclass within the indication cohort.

## Table 19: Intention-To-Treat and As-Treated Follow-Up Period by Indication and Opioid Users for Alberta for the Feasibility Study

| Indication and opioid users | Total N | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| **Postsurgical** | | | |
| Nonusers | 583,269 | 3,357,807 | 1,603,709 |
| New users | 35,533 | 212,482 | 4,121 |
| Prevalent users | 42,027 | 226,791 | 26,447 |
| **Trauma** | | | |
| Nonusers | 2,292,067 | 16,088,511 | 8,732,531 |
| New users | 141,678 | 970,468 | 15,157 |
| Prevalent users | 104,006 | 710,887 | 103,917 |
| **Dental** | | | |
| Nonusers | 5,197 | 26,637 | 12,720 |

| Indication and opioid users | Total N | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| New users | 334 | 1,729 | 65 |
| Prevalent users | 575 | 2,621 | 520 |
| **Other pain** | | | |
| Nonusers | 2,695,818 | 18,802,257 | 10,303,691 |
| New users | 100,865 | 686,859 | 15,337 |
| Prevalent users | 93,434 | 653,559 | 105,163 |

Note: Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

## Table 20: Intention-To-Treat and As-Treated Follow-Up Period by Indication and Opioid Users for Manitoba for the Feasibility Study

| Indication and opioid users | Total N | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| **Postsurgical** | | | |
| Nonusers | 243,481 | 2,138,495 | 1,108,454 |
| New users | 164,607 | 1,569,481 | 15,115 |
| Prevalent users | 30,103 | 270,743 | 31,147 |
| **Trauma** | | | |
| Nonusers | 607,694 | 5,994,875 | 3,095,188 |
| New users | 60,327 | 603,163 | 5,768 |
| Prevalent users | 38,470 | 353,681 | 58,436 |
| **Dental** | | | |
| Nonusers | 2,845 | 23,783 | 12,918 |
| New users | 4,816 | 43,732 | 412 |
| Prevalent users | 1,601 | 12,623 | 1,902 |
| **Other pain** | | | |
| Nonusers | 586,476 | 5,460,784 | 2,835,821 |
| New users | 25,554 | 259,007 | 3,363 |
| Prevalent users | 30,732 | 277,109 | 61,352 |

Note: Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

## Table 21: Intention-To-Treat and As-Treated Follow-Up Period by Indication and Opioid Users for Ontario for the Feasibility Study

| Indication and opioid users | Total N | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| **Postsurgical** | | | |
| Nonusers | 832,058 | 4,191,744 | 2,831,980 |
| New users | 637,848 | 3,364,512 | 55,776 |
| Prevalent users | 114,422 | 599,393 | 99,970 |
| **Trauma** | | | |
| Nonusers | 1,759,321 | 9,184,126 | 6,901,269 |
| New users | 128,175 | 689,101 | 9,538 |
| Prevalent users | 39,965 | 197,971 | 61,300 |
| **Dental** | | | |
| Nonusers | 17,088 | 80,133 | 50,620 |
| New users | 25,243 | 130,183 | 2,143 |
| Prevalent users | 9,679 | 47,182 | 16,028 |
| **Other pain** | | | |
| Nonusers | 1,579,800 | 8,084,191 | 5,821,344 |
| New users | 163,618 | 862,010 | 11,956 |
| Prevalent users | 73,560 | 360,367 | 101,809 |

Note: Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

## Table 22: Intention-To-Treat and As-Treated Follow-Up Period by Indication and Opioid Users for Saskatchewan for the Feasibility Study

| Indication and opioid users | Total N | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| **Postsurgical** | | | |
| Nonusers | 364,855 | 2,849,675 | 1,710,075 |
| New users | 113,985 | 765,712 | 162,321 |
| Prevalent users | 22,972 | 141,232 | 46,012 |
| **Trauma** | | | |
| Nonusers | 613,938 | 5,301,606 | 3,291,604 |
| New users | 48,918 | 380,046 | 28,249 |
| Prevalent users | 18,161 | 123,668 | 33,820 |
| **Dental** | | | |
| Nonusers | 3,149 | 25,957 | 16,618 |
| New users | 1,422 | 9,567 | 523 |

| Indication and opioid users | Total N | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| Prevalent users | 427 | 2,438 | 552 |
| **Other pain** | | | |
| Nonusers | 581,650 | 4,428,213 | 2,800,706 |
| New users | 25,476 | 171,004 | 11,578 |
| Prevalent users | 19,956 | 122,581 | 37,531 |

Note: Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

## Table 23: Intention-To-Treat and As-Treated Follow-Up Period by Indication and Opioid Users for US Merative MarketScan for the Feasibility Study

| Indication and opioid users | Total N | Intention-to-treat follow-up (person-years) | As-treated follow-up (person-years) |
|---|---|---|---|
| **Postsurgical** | | | |
| Nonusers | 22,846,334 | 63,346,350 | 37,393,128 |
| New users | 5,037,562 | 14,746,591 | 454,816 |
| Prevalent users | 1,809,172 | 5,236,412 | 460,937 |
| **Trauma** | | | |
| Nonusers | 34,603,324 | 86,403,165 | 56,665,269 |
| New users | 4,775,529 | 13,154,899 | 330,570 |
| Prevalent users | 1,955,599 | 5,244,499 | 1,239,234 |
| **Dental** | | | |
| Nonusers | 126,993 | 292,937 | 212,413 |
| New users | 53,414 | 131,806 | 4,143 |
| Prevalent users | 20,186 | 49,771 | 3,593 |
| **Other pain** | | | |
| Nonusers | 43,972,255 | 110,501,321 | 71,187,453 |
| New users | 4,540,407 | 11,692,925 | 414,512 |
| Prevalent users | 2,086,132 | 5,436,983 | 1,553,066 |

Note: Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

## Table 24: Incident Rates of Diverticulitis by Indications and Outcome Definitions, by Site for the Feasibility Study

| Indication[a] and outcome | Alberta | | Manitoba[b] | | Ontario | | Saskatchewan[c] | | US Merative MarketScan[d] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total events | Incidence rate | Total events | Incidence rate | Total events | Incidence rate | Total events | Incidence rate | Total events | Incidence rate |
| **Postsurgical** | | | | | | | | | | |
| Outcome 1 | 12,308 | 32.4 | 14,459 | 36.3 | 20,057 | 24.6 | 17,623 | 46.9 | — | — |
| Outcome 2 | 1,241 | 3.3 | 2,630 | 6.6 | 4,138 | 5.1 | — | — | 57,361 | 6.9 |
| **Trauma** | | | | | | | | | | |
| Outcome 1 | 37,836 | 21.3 | 18,276 | 26.3 | 13,539 | 13.4 | 20,366 | 35.1 | — | — |
| Outcome 2 | 4,040 | 2.3 | 3,491 | 5.0 | 2,946 | 2.9 | — | — | 61,732 | 5.9 |
| **Dental** | | | | | | | | | | |
| Outcome 1 | 76 | 24.5 | 142 | 17.7 | 546 | 21.2 | 64 | 16.9 | — | — |
| Outcome 2 | 6 | 1.9 | 32 | 4.0 | 129 | 5.0 | — | — | 218 | 4.6 |
| **Other pain** | | | | | | | | | | |
| Outcome 1 | 42,032 | 20.9 | 15,951 | 26.6 | 17,601 | 18.9 | 17,093 | 36.2 | — | — |
| Outcome 2 | 4,498 | 2.2 | 3,046 | 5.1 | 3,520 | 3.8 | — | — | 78,848 | 6.2 |

ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

[b]Manitoba data were not available for ED visits for outcome 1.

[c]Saskatchewan data were not available for outcome 2.

[d]US Merative MarketScan data were not available for outcome 1.

## Table 25: Average Risk of Diverticulitis by Indication and Outcome Definition for Alberta for the Feasibility Study

| Indication[a] and outcome | Average 30-day risk | Average 180-day risk | Average 730-day risk |
|---|---|---|---|
| **Postsurgical** | | | |
| Outcome 1 | 0.00032 | 0.00140 | 0.00480 |
| Outcome 2 | 0.00005 | 0.00018 | 0.00058 |
| **Trauma** | | | |
| Outcome 1 | 0.00011 | 0.00069 | 0.00268 |
| Outcome 2 | 0.00002 | 0.00008 | 0.00033 |
| **Dental** | | | |
| Outcome 1 | 0.00050 | 0.00120 | 0.00520 |
| Outcome 2 | 0.00000 | 0.00000 | 0.00077 |
| **Other pain** | | | |
| Outcome 1 | 0.00013 | 0.00073 | 0.00265 |
| Outcome 2 | 0.00001 | 0.00007 | 0.00033 |

ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

## Table 26: Average Risk of Diverticulitis by Indication and Outcome Definition for Manitoba for the Feasibility Study

| Indication[a] and outcome[b] | Average 30-day risk | Average 180-day risk | Average 730-day risk |
|---|---|---|---|
| **Postsurgical** | | | |
| Outcome 1 | 0.00024 | 0.00186 | 0.00662 |
| Outcome 2 | 0.00006 | 0.00033 | 0.00114 |
| **Trauma** | | | |
| Outcome 1 | 0.00020 | 0.00110 | 0.00417 |
| Outcome 2 | 0.00005 | 0.00022 | 0.00080 |
| **Dental** | | | |
| Outcome 1 | 0.00011 | 0.00066 | 0.00338 |
| Outcome 2 | 0.00000 | 0.00011 | 0.00045 |
| **Other pain** | | | |
| Outcome 1 | 0.00022 | 0.00127 | 0.00440 |
| Outcome 2 | 0.00002 | 0.00021 | 0.00082 |

ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

[b]Manitoba data were not available for ED visits for outcome 1.

## Table 27: Average Risk of Diverticulitis by Indication and Outcome Definition for Ontario for the Feasibility Study

| Indication[a] and outcome | Average 30-day risk | Average 180-day risk | Average 730-day risk |
|---|---|---|---|
| **Postsurgical** | | | |
| Outcome 1 | 0.00025 | 0.00118 | 0.00416 |
| Outcome 2 | 0.00007 | 0.00029 | 0.00098 |
| **Trauma** | | | |
| Outcome 1 | 0.00010 | 0.00053 | 0.00213 |
| Outcome 2 | 0.00003 | 0.00014 | 0.00052 |
| **Dental** | | | |
| Outcome 1 | 0.00021 | 0.00097 | 0.00364 |
| Outcome 2 | 0.00006 | 0.00025 | 0.00101 |
| **Other pain** | | | |
| Outcome 1 | 0.00018 | 0.00083 | 0.00316 |
| Outcome 2 | 0.00004 | 0.00019 | 0.00071 |

ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

## Table 28: Average Risk of Diverticulitis by Indication and Outcome Definition for Saskatchewan for the Feasibility Study

| Indication[a] and outcome[b] | Average 30-day risk | Average 180-day risk | Average 730-day risk |
|---|---|---|---|
| **Postsurgical** | | | |
| Outcome 1 | 0.00022 | 0.00228 | 0.00942 |
| Outcome 2 | — | — | — |
| **Trauma** | | | |
| Outcome 1 | 0.00031 | 0.00162 | 0.00632 |
| Outcome 2 | — | — | — |
| **Dental** | | | |
| Outcome 1 | 0 | 0.00041 | 0.00287 |
| Outcome 2 | — | — | — |
| **Other pain** | | | |
| Outcome 1 | 0.00036 | 0.00192 | 0.00656 |
| Outcome 2 | — | — | — |

ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

[b]Saskatchewan data were not available for outcome 2.

## Table 29: Average Risk of Diverticulitis by Indication and Outcome Definition For US Merative MarketScan for the Feasibility Study

| Indication[a] and outcome[b] | Average 30-day risk | Average 180-day risk | Average 730-day risk |
|---|---|---|---|
| **Postsurgical** | | | |
| Outcome 1 | — | — | — |
| Outcome 2 | 0.00007 | 0.00034 | 0.00127 |
| **Trauma** | | | |
| Outcome 1 | — | — | — |
| Outcome 2 | 0.00005 | 0.00027 | 0.00107 |
| **Dental** | | | |
| Outcome 1 | — | — | — |
| Outcome 2 | 0.00004 | 0.00016 | 0.00078 |
| **Other pain** | | | |
| Outcome 1 | — | — | — |
| Outcome 2 | 0.00006 | 0.00030 | 0.00114 |

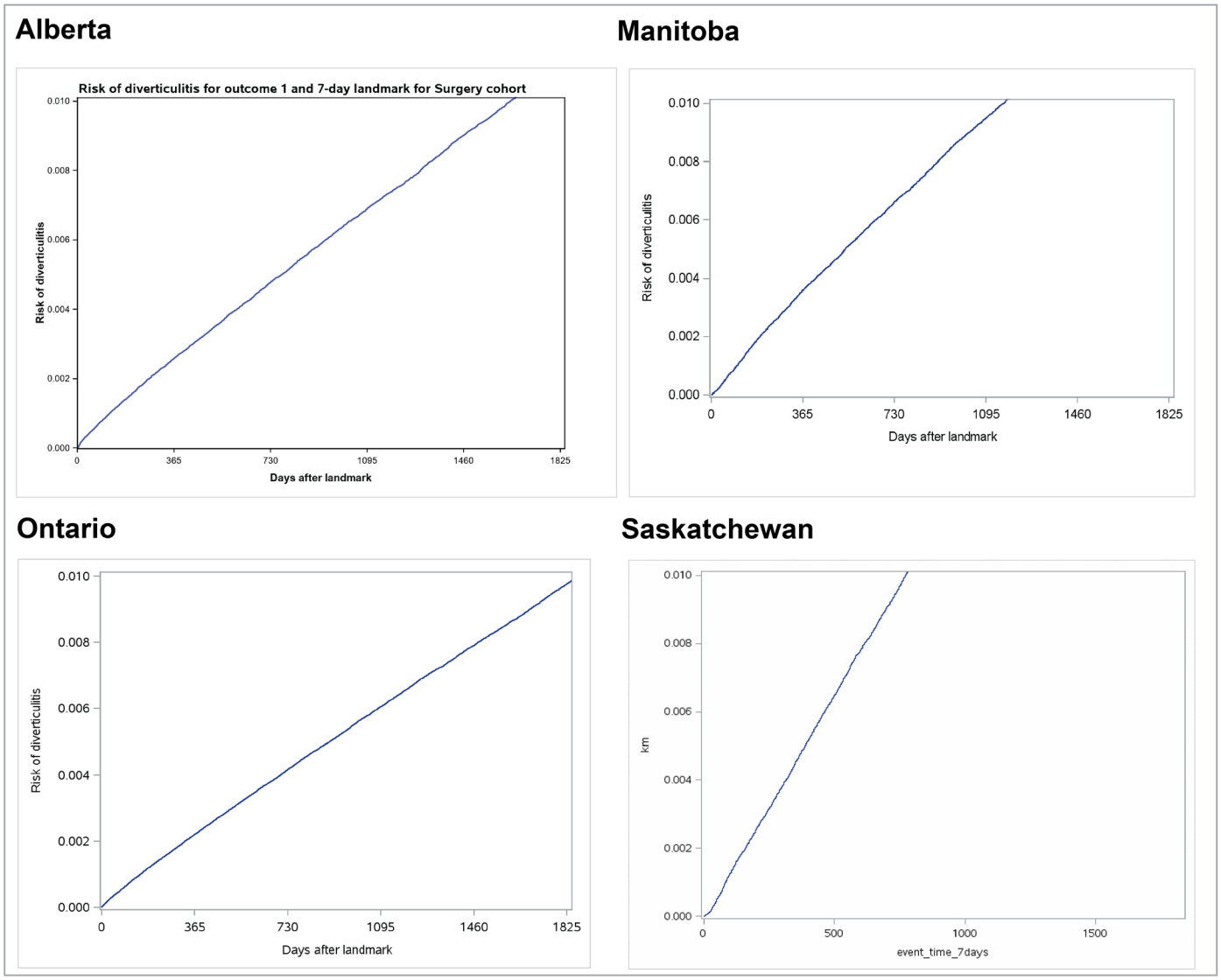
ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

[a]Postsurgical and dental indication: 7-day landmark and 90-day lookback period; trauma and other pain indication: 30-day landmark and 90-day lookback period.

[b]US Merative MarketScan data not available for outcome 1.

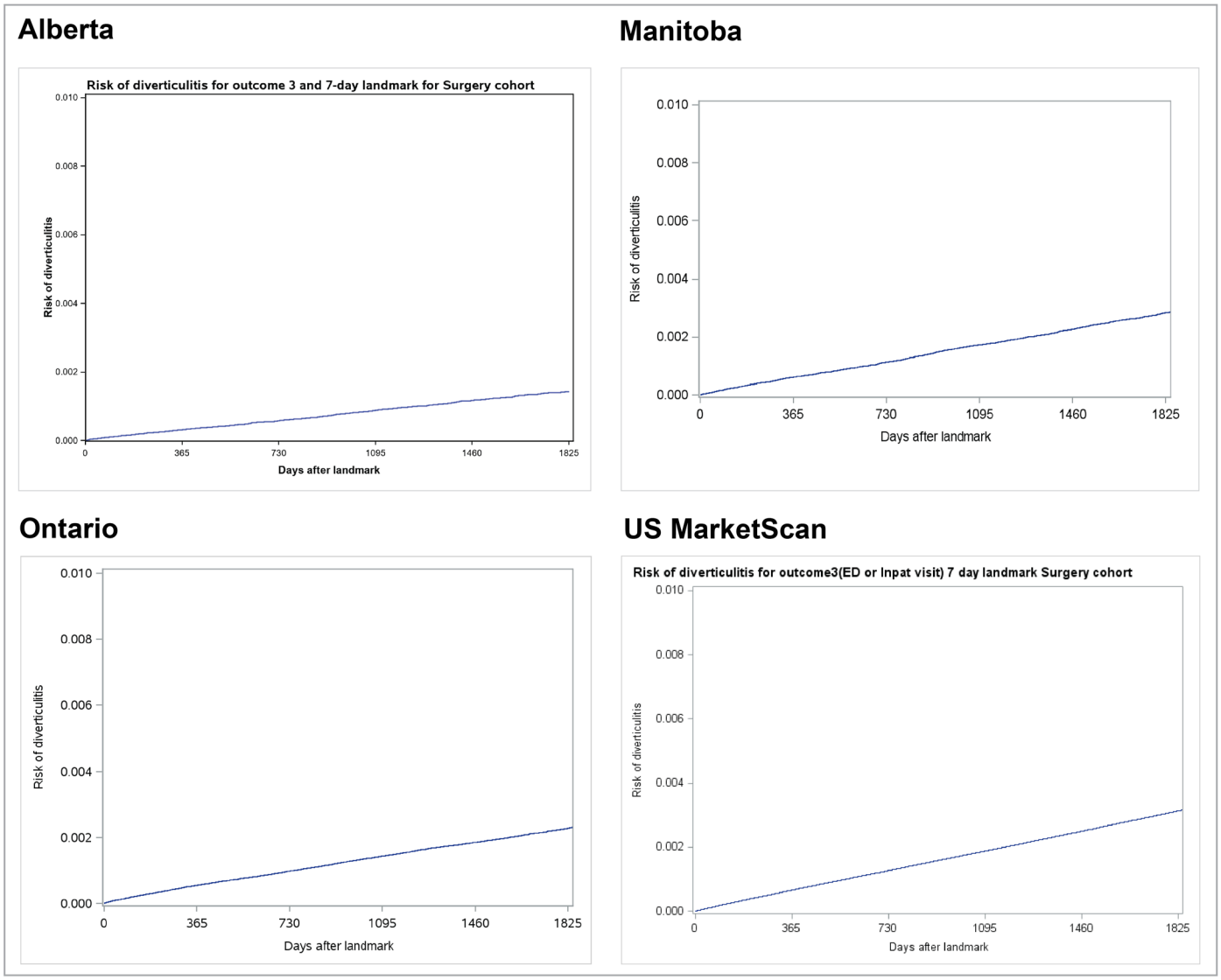
## Figure 9: Intention-to-Treat Incidence Curves for Outcome 1 in Feasibility Postsurgical Cohort




ED = emergency department.

Note: Outcome 1 is ED or inpatient visit for diverticulitis.

## Figure 10: Intention-to-Treat Incidence Curves for Outcome 2 in Feasibility Postsurgical Cohort




Note: Outcome 2 is inpatient visit and CT scan.

# Appendix 3: Additional Findings for Postsurgical Indication

## Table 30: Additional Baseline Characteristics of Opioid New Users and Nonusers Before and After Odds Weighting for the Postsurgical Indication Cohort, by Region

| Characteristic (%) | Canada | | | UK CPRD | | | US Merative MarketScan | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 1,434,490 | Nonusers N = 2,858,751 | Nonusers N = 1,434,756 | New users N = 76,462 | Nonusers N = 599,417 | Nonusers N = 76,436 | New users N = 3,198,147 | Nonusers N = 13,382,299 | Nonusers N = 3,196,171 |
| **Site** | | | | | | | | | |
| Alberta | 2.5 | 20.1 | 2.5 | — | — | — | — | — | — |
| British Columbia | 35.5 | 31.8 | 35.5 | — | — | — | — | — | — |
| Manitoba | 11.3 | 8.3 | 11.2 | — | — | — | — | — | — |
| Ontario | 43.6 | 28.4 | 43.7 | — | — | — | — | — | — |
| Saskatchewan | 7.2 | 11.3 | 7.1 | — | — | — | — | — | — |
| **Comorbidities** | | | | | | | | | |
| History of irritable bowel syndrome | 1.2 | 1.0 | 1.2 | 8.7 | 7.6 | 8.7 | 1.1 | 1.1 | 1.1 |
| History of Crohn disease | 0.6 | 0.6 | 0.6 | 0.5 | 0.5 | 0.5 | 0.4 | 0.3 | 0.4 |
| Transient ischemic attack | 0.2 | 0.7 | 0.2 | 2.7 | 2.4 | 2.7 | 0.2 | 0.3 | 0.2 |
| Dementia | 0.6 | 2.0 | 0.6 | 1.8 | 2.2 | 1.8 | 0.1 | 0.2 | 0.1 |
| Peptic ulcer disease | 0.8 | 1.1 | 0.8 | 4.5 | 3.4 | 4.5 | 0.4 | 0.3 | 0.4 |
| Liver disease | 0.5 | 0.7 | 0.5 | 0.4 | 0.3 | 0.4 | 1.1 | 0.8 | 1.1 |

| Characteristic (%) | Canada | | | UK CPRD | | | US Merative MarketScan | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 1,434,490 | Nonusers N = 2,858,751 | Nonusers N = 1,434,756 | New users N = 76,462 | Nonusers N = 599,417 | Nonusers N = 76,436 | New users N = 3,198,147 | Nonusers N = 13,382,299 | Nonusers N = 3,196,171 |
| Hemiplegia | 0.0 | 0.3 | 0.1 | 0.7 | 0.7 | 0.7 | 0.0 | 0.0 | 0.0 |
| **Race[a]** | | | | | | | | | |
| First Nations or Indigenous | — | — | — | 0.0 | 0.0 | 0.0 | — | — | — |
| Asian | — | — | — | 3.9 | 3.3 | 3.9 | — | — | — |
| Black | — | — | — | 1.8 | 1.9 | 1.8 | — | — | — |
| White | — | — | — | 89.2 | 85.2 | 89.2 | — | — | — |
| Other | — | — | — | 1.2 | 1.5 | 1.1 | — | — | — |
| Unknown | — | — | — | 3.9 | 8.1 | 3.9 | — | — | — |
| **Ethnicity[a]** | | | | | | | | | |
| Hispanic | — | — | — | 0.0 | 0.0 | 0.0 | — | — | — |
| Non-Hispanic | — | — | — | 96.1 | 91.9 | 96.1 | — | — | — |
| Unknown | — | — | — | 3.9 | 8.1 | 3.9 | — | — | — |
| **Smoking[a]** | | | | | | | | | |
| Current smoker | — | — | — | 23.9 | 22.7 | 23.8 | — | — | — |
| Past smoker | — | — | — | 26.4 | 23.4 | 26.4 | — | — | — |
| Never smoker | — | — | — | 44.2 | 46.6 | 44.2 | — | — | — |
| Unknown | — | — | — | 5.6 | 7.3 | 5.6 | — | — | — |
| **Body mass index[a]** | | | | | | | | | |
| Underweight | — | — | — | 0.8 | 1.5 | 0.8 | — | — | — |

| Characteristic (%) | Canada | | | UK CPRD | | | US Merative MarketScan | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 1,434,490 | Nonusers N = 2,858,751 | Nonusers N = 1,434,756 | New users N = 76,462 | Nonusers N = 599,417 | Nonusers N = 76,436 | New users N = 3,198,147 | Nonusers N = 13,382,299 | Nonusers N = 3,196,171 |
| Normal weight | — | — | — | 21.8 | 31.7 | 21.8 | — | — | — |
| Overweight | — | — | — | 35.2 | 32 | 35.2 | — | — | — |
| Obese | — | — | — | 32.6 | 22.2 | 32.6 | — | — | — |
| Unknown | — | — | — | 9.6 | 12.6 | 9.6 | — | — | — |

CPRD = Clinical Practice Research Datalink.

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]Data only available in the UK CPRD.

Note: This table has not been copy-edited.

## Table 31: Baseline Characteristics of Opioids New Users and Prevalent Users Before and After Odds Weighting for the Postsurgical Indication Cohort

| Characteristic (%) | Unweighted | | Odds weighted |
|---|---|---|---|
| | New users N = 4,709,099 | Prevalent users N = 1,534,844 | Prevalent users N = 4,702,862 |
| **Calendar year of cohort entry[a]** | | | |
| 2004 to 2007 | 9.8 | 10.5 | 9.9 |
| 2008 to 2011 | 29.1 | 34.5 | 29.2 |
| 2012 to 2015 | 30.3 | 31.9 | 30.3 |
| 2016 to 2020 | 30.7 | 23.1 | 30.6 |
| **Site** | | | |
| Alberta | 0.8 | 2.7 | 0.8 |
| British Columbia | 10.8 | 6.3 | 10.8 |
| Manitoba | 3.4 | 1.9 | 3.4 |
| Ontario | 13.3 | 7.4 | 13.3 |
| Saskatchewan | 2.2 | 1.3 | 2.2 |
| UK CPRD | 1.6 | 7.3 | 1.6 |
| US Merative MarketScan | 67.9 | 73.1 | 67.9 |
| **Age (years)** | | | |
| 18 to 39 | 38.8 | 25.7 | 38.5 |
| 40 to 64 | 49.3 | 58.6 | 49.4 |
| 65 to 79 | 10.1 | 12.7 | 10.0 |
| 80+ | 1.7 | 3.0 | 2.0 |
| **Sex** | | | |
| Males | 39.9 | 41.2 | 39.8 |
| Females | 60.1 | 58.8 | 60.2 |
| **Income quintile[b]** | | | |
| First (lowest) | 17.5 | 20.9 | 17.4 |
| Second | 19.0 | 19.3 | 19.1 |
| Third | 20.0 | 19.9 | 19.9 |
| Fourth | 20.3 | 19.1 | 20.3 |
| Fifth (highest) | 20.5 | 19.0 | 20.5 |
| **Comorbidities** | | | |
| History of irritable bowel syndrome | 1.3 | 2.3 | 1.3 |
| History of Crohn disease | 0.5 | 0.8 | 0.5 |
| History of diverticulitis or diverticulosis | 1.8 | 3.2 | 1.9 |

| Characteristic (%) | Unweighted | | Odds weighted |
|---|---|---|---|
| | New users N = 4,709,099 | Prevalent users N = 1,534,844 | Prevalent users N = 4,702,862 |
| History of myocardial infarction | 1.1 | 1.3 | 1.1 |
| History of congestive heart failure | 0.9 | 1.7 | 0.9 |
| Peripheral vascular disease | 0.9 | 1.6 | 0.9 |
| Cerebrovascular accident | 1.2 | 2.0 | 1.2 |
| Transient ischemic attack | 0.3 | 0.6 | 0.3 |
| Dementia | 0.2 | 0.5 | 0.3 |
| Chronic obstructive pulmonary disease | 3.1 | 6.6 | 3.1 |
| Peptic ulcer disease | 0.6 | 1.4 | 0.6 |
| Liver disease | 0.9 | 1.6 | 0.9 |
| Diabetes mellitus | 8.7 | 12.8 | 8.8 |
| Hemiplegia | 0.0 | 0.2 | 0.0 |
| Chronic kidney disease | 1.1 | 2.6 | 1.2 |
| Current tumour | 9.1 | 8.6 | 9.3 |
| **Subclass of indication[c]** | | | |
| Common excision | 9.5 | 6.8 | 8.8 |
| Knee, hip, or shoulder surgery | 7.8 | 13.8 | 7.8 |
| Hernia repair | 4.3 | 1.7 | 4.3 |
| Caesarean section | 13.0 | 2.4 | 11.9 |
| Other surgery | 68.0 | 76.3 | 68.0 |
| **Race[d]** | | | |
| First Nations or Indigenous | 0.0 | 0.0 | 0.0 |
| Asian | 3.9 | 2.0 | 3.7 |
| Black | 1.8 | 1.2 | 1.8 |
| White | 89.2 | 93.6 | 89.6 |
| Other | 1.2 | 0.7 | 1.1 |
| Unknown | 3.9 | 2.5 | 3.8 |
| **Ethnicity[d]** | | | |
| Hispanic | 0.0 | 0.0 | 0.0 |
| Non-Hispanic | 96.1 | 97.5 | 96.2 |
| Unknown | 3.9 | 2.5 | 3.8 |
| **Smoking[d]** | | | |
| Current smoker | 23.9 | 23.9 | 24.1 |
| Past smoker | 26.4 | 29.4 | 26.6 |

| Characteristic (%) | Unweighted | | Odds weighted |
|---|---|---|---|
| | New users N = 4,709,099 | Prevalent users N = 1,534,844 | Prevalent users N = 4,702,862 |
| Never smoker | 44.2 | 40.4 | 43.8 |
| Unknown | 5.6 | 6.3 | 5.6 |
| **Body mass index[d]** | | | |
| Underweight | 0.8 | 0.8 | 0.8 |
| Normal weight | 21.8 | 17.9 | 21.4 |
| Overweight | 35.2 | 32.6 | 35.3 |
| Obese | 32.6 | 40.2 | 33.0 |
| Unknown | 9.6 | 8.6 | 9.5 |

CPRD = Clinical Practice Research Datalink.

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]Alberta data were available as of 2008, Ontario as of 2013, and US Merative MarketScan as of 2006.

[b]Site-specific definition; missing values not reported and account for discrepancies between income quintile categories and overall cohort totals. Data not available in the US Merative MarketScan. Data not reported for British Columbia, which was able to adjust for low income versus not low income (or missing) rather than quintiles.

[c]Other surgery subclass not included in the UK CPRD. Patients were allowed to enter multiple subclasses in the US Merative MarketScan.

[d]Race, ethnicity, smoking, and body mass index data were only available in the UK CPRD.

Note: This table has not been copy-edited.

## Table 32: Baseline Characteristics of Opioids New Users, Nonusers, and Prevalent Users Before and After IPTW Weighting for the Postsurgical Indication Cohort

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 966,764 | Nonusers N = 1,972,708 | Prevalent users N = 273,992 | New users N = 3,122,742 | Nonusers N = 3,073,631 | Prevalent users N = 3,110,275 |
| **Calendar year of cohort entry[a]** | | | | | | |
| 2004 to 2007 | 8.2 | 16.6 | 13.3 | 14.2 | 13.5 | 13.8 |
| 2008 to 2011 | 8.9 | 14.4 | 14.8 | 12.5 | 12.4 | 12.5 |
| 2012 to 2015 | 34.1 | 28.9 | 32.7 | 30.8 | 31.0 | 30.8 |
| 2016 to 2020 | 48.8 | 40.0 | 39.2 | 42.5 | 43.1 | 42.9 |
| **Site** | | | | | | |
| Manitoba | 16.7 | 12.0 | 10.8 | 13.9 | 13.9 | 13.8 |
| Ontario | 64.7 | 41.2 | 41.3 | 50.0 | 50.6 | 49.9 |
| Saskatchewan | 10.6 | 16.4 | 7.2 | 14.8 | 14.5 | 14.4 |
| UK CPRD | 7.9 | 30.4 | 40.6 | 21.4 | 21.0 | 22.0 |
| **Age (years)** | | | | | | |
| 18 to 39 | 32.3 | 22.7 | 14.3 | 22.3 | 22.3 | 22.5 |

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 966,764 | Nonusers N = 1,972,708 | Prevalent users N = 273,992 | New users N = 3,122,742 | Nonusers N = 3,073,631 | Prevalent users N = 3,110,275 |
| 40 to 64 | 45.7 | 35.3 | 45.6 | 40.0 | 40.2 | 40.0 |
| 65 to 79 | 18.9 | 30.2 | 31.4 | 28.0 | 28.0 | 27.8 |
| 80+ | 3.1 | 11.8 | 8.7 | 9.7 | 9.6 | 9.7 |
| **Sex** | | | | | | |
| Males | 44.8 | 40.2 | 42.0 | 43.3 | 43.1 | 42.6 |
| Females | 55.2 | 59.8 | 58.0 | 56.7 | 56.9 | 57.4 |
| **Income quintile[b]** | | | | | | |
| First (lowest) | 22.7 | 20.7 | 22.6 | 22.7 | 30.2 | 22.9 |
| Second | 20.5 | 20.4 | 20.5 | 20.5 | 21.3 | 20.6 |
| Third | 18.8 | 19.1 | 18.8 | 18.8 | 17.2 | 18.8 |
| Fourth | 17.5 | 18.1 | 17.5 | 17.5 | 14.7 | 17.3 |
| Fifth (highest) | 16.6 | 18.0 | 16.7 | 16.6 | 12.7 | 16.5 |
| **Comorbidities** | | | | | | |
| History of irritable bowel syndrome | 2.2 | 3.4 | 5.7 | 3.1 | 3.1 | 3.1 |
| History of Crohn disease | 0.5 | 0.5 | 1.0 | 0.6 | 0.6 | 0.5 |
| History of diverticulitis or diverticulosis | 2.8 | 4.2 | 7.7 | 4.4 | 4.4 | 4.3 |
| History of myocardial infarction | 3.3 | 7.2 | 4.9 | 7.3 | 6.2 | 6.2 |
| History of congestive heart failure | 1.5 | 4.0 | 4.3 | 4.1 | 3.5 | 3.6 |
| Peripheral vascular disease | 1.0 | 2.1 | 3.4 | 2.1 | 2.0 | 2.0 |
| Cerebrovascular accident | 1.3 | 3.2 | 3.8 | 3.2 | 2.9 | 2.8 |
| Transient ischemic attack | 0.4 | 1.0 | 1.6 | 0.9 | 1.0 | 0.9 |
| Dementia | 0.7 | 2.0 | 1.8 | 2.0 | 1.7 | 1.9 |
| Chronic obstructive pulmonary disease | 3.6 | 5.2 | 8.8 | 5.6 | 5.3 | 5.2 |
| Peptic ulcer disease | 1.0 | 1.7 | 3.8 | 1.9 | 1.8 | 1.8 |
| Liver disease | 0.4 | 0.4 | 0.9 | 0.5 | 0.5 | 0.5 |
| Diabetes mellitus | 10.8 | 14.6 | 16.5 | 15.0 | 14.3 | 14.1 |
| Hemiplegia | 0.1 | 0.4 | 0.5 | 0.5 | 0.3 | 0.3 |
| Chronic kidney disease | 1.9 | 4.8 | 7.6 | 4.8 | 4.5 | 4.4 |
| Current tumour | 12.3 | 11.9 | 14.1 | 13.5 | 13.1 | 13.2 |
| **Subclass of indication[c]** | | | | | | |
| Common excision | 5.7 | 17.4 | 7.4 | 12.9 | 12.4 | 13.4 |
| Knee, hip, or shoulder surgery | 20.3 | 14.6 | 47.2 | 19.7 | 20.0 | 19.7 |

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 966,764 | Nonusers N = 1,972,708 | Prevalent users N = 273,992 | New users N = 3,122,742 | Nonusers N = 3,073,631 | Prevalent users N = 3,110,275 |
| Hernia repair | 11.5 | 4.5 | 4.9 | 6.8 | 6.9 | 6.8 |
| Caesarean section | 6.8 | 10.9 | 1.2 | 5.8 | 5.9 | 5.7 |
| Other surgery | 55.7 | 52.7 | 39.3 | 54.8 | 54.9 | 54.3 |
| **Race[d]** | | | | | | |
| First Nations or Indigenous | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Asian | 3.9 | 3.3 | 2.0 | 1.9 | 1.9 | 1.9 |
| Black | 1.8 | 1.9 | 1.2 | 1.0 | 1.0 | 1.0 |
| White | 89.2 | 85.2 | 93.6 | 90.6 | 91.3 | 89.0 |
| Other | 1.2 | 1.5 | 0.7 | 0.9 | 0.9 | 0.9 |
| Unknown | 3.9 | 8.1 | 2.5 | 5.5 | 4.9 | 7.2 |
| **Ethnicity[d]** | | | | | | |
| Hispanic | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Non-Hispanic | 96.1 | 91.9 | 97.5 | 94.5 | 95.1 | 92.8 |
| Unknown | 3.9 | 8.1 | 2.5 | 5.5 | 4.9 | 7.2 |
| **Smoking[d]** | | | | | | |
| Current smoker | 23.9 | 22.7 | 23.9 | 23.1 | 23.7 | 23.0 |
| Past smoker | 26.4 | 23.4 | 29.4 | 26.1 | 26.8 | 25.8 |
| Never smoker | 44.2 | 46.6 | 40.4 | 43.9 | 42.7 | 44.5 |
| Unknown | 5.6 | 7.3 | 6.3 | 6.8 | 6.8 | 6.8 |
| **Body mass index[d]** | | | | | | |
| Underweight | 0.8 | 1.5 | 0.8 | 1.1 | 1.0 | 1.1 |
| Normal weight | 21.8 | 31.7 | 17.9 | 26.2 | 25.5 | 26.9 |
| Overweight | 35.2 | 32.0 | 32.6 | 34.1 | 34.5 | 33.9 |
| Obese | 32.6 | 22.2 | 40.2 | 27.5 | 28.5 | 26.8 |
| Unknown | 9.6 | 12.6 | 8.6 | 11.1 | 10.5 | 11.3 |

CPRD = Clinical Practice Research Datalink; IPTW = inverse probability of treatment weights.

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]Ontario data were available as of 2013.

[b]Site-specific definition. Missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

[c]Other surgery subclass not included in the UK CPRD.

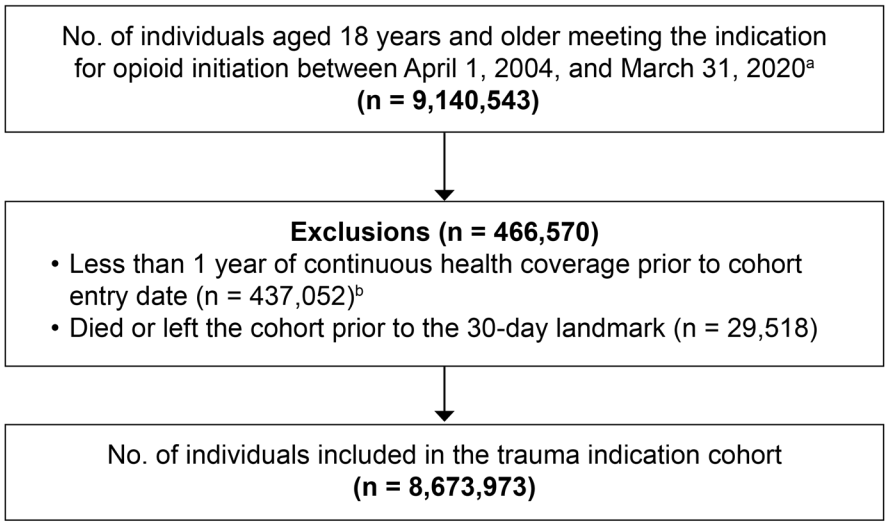
[d]Race, ethnicity, smoking, and body mass index data only available in UK CPRD.

Note: This table has not been copy-edited.

# Appendix 4: Main Findings for Trauma and Other Pain Indications

Please note that this appendix has not been copy-edited.

## Figure 11: Flow Chart for Trauma Indication Study Cohort Construction

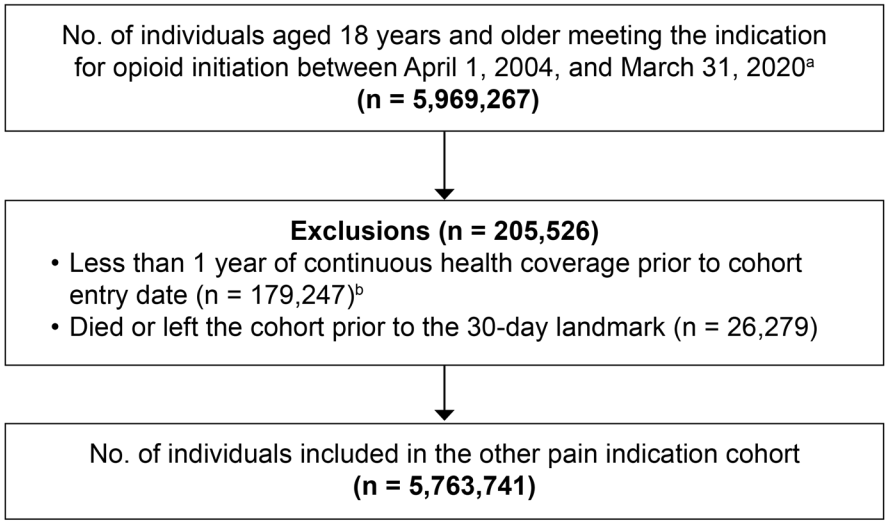



Note: Data aggregated for 5 Canadian provinces (Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan).

[a]Data were available as of 2008 for Alberta and 2013 for Ontario.

[b]Individuals with less than 365 days of health coverage before cohort entry date could not be identified in Alberta due to the unavailability of start of coverage date.

## Figure 12: Flow Chart for Other Pain Indication Study Cohort Construction




Note: Data aggregated for 4 Canadian provinces (Alberta, Manitoba, Ontario, and Saskatchewan).

[a]Data were available as of 2008 for Alberta and 2013 for Ontario.

[b]Individuals with less than 365 days of health coverage before cohort entry date could not be identified in Alberta due to the unavailability of start of coverage date.

## Table 33: Baseline Characteristics of Opioids New Users, Nonusers, and Prevalent Users Before and After Odds Weighting for the Trauma Indication Cohort

| Characteristic (%) | New users versus nonusers | | | New users versus prevalent users | | |
|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 591,180 | Nonusers N = 7,812,690 | Nonusers N = 591,234 | New users N = 591,180 | Prevalent users N = 270,103 | Prevalent users N = 587,597 |
| **Calendar year of cohort entry[a]** | | | | | | |
| 2004 to 2007 | 22.1 | 20.7 | 22.1 | 22.1 | 23.6 | 21.9 |
| 2008 to 2011 | 26.3 | 26.6 | 26.3 | 26.3 | 33.1 | 26.6 |
| 2012 to 2015 | 28.2 | 26.6 | 28.2 | 28.2 | 24.8 | 28.2 |
| 2016 to 2020 | 23.4 | 26.1 | 23.3 | 23.4 | 18.4 | 23.3 |
| **Site** | | | | | | |
| Alberta | 25.0 | 29.1 | 25.0 | 25.0 | 37.5 | 25.0 |
| British Columbia | 37.3 | 35.8 | 37.3 | 37.3 | 28.3 | 37.3 |
| Manitoba | 9.9 | 7.5 | 9.9 | 9.9 | 13.8 | 9.9 |
| Ontario | 20.1 | 20.3 | 20.1 | 20.1 | 14.1 | 20.0 |
| Saskatchewan | 7.8 | 7.4 | 7.8 | 7.8 | 6.3 | 7.7 |
| **Age (years)** | | | | | | |
| 18 to 39 | 34.9 | 41.5 | 34.8 | 34.9 | 21.7 | 34.6 |
| 40 to 64 | 44.1 | 40.9 | 44.2 | 44.1 | 50.3 | 43.4 |
| 65 to 79 | 14.8 | 12.4 | 14.7 | 14.8 | 18.6 | 14.9 |
| 80+ | 6.2 | 5.2 | 6.3 | 6.2 | 9.4 | 7.0 |
| **Sex** | | | | | | |
| Males | 52.6 | 48.4 | 52.6 | 52.6 | 46.6 | 52.1 |
| Females | 47.4 | 51.6 | 47.4 | 47.4 | 53.4 | 47.9 |

| Characteristic (%) | New users versus nonusers | | | New users versus prevalent users | | |
|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 591,180 | Nonusers N = 7,812,690 | Nonusers N = 591,234 | New users N = 591,180 | Prevalent users N = 270,103 | Prevalent users N = 587,597 |
| **Income quintile[b]** | | | | | | |
| First (lowest) | 14.2 | 13.3 | 14.2 | 14.2 | 21.7 | 14.3 |
| Second | 12.9 | 13.1 | 12.9 | 12.9 | 15.3 | 12.9 |
| Third | 11.8 | 12.3 | 11.8 | 11.8 | 12.3 | 11.8 |
| Fourth | 11.0 | 11.6 | 11.0 | 11.0 | 10.6 | 10.9 |
| Fifth (Highest) | 10.4 | 11.6 | 10.4 | 10.4 | 9.1 | 10.3 |
| **Comorbidities** | | | | | | |
| History of irritable bowel syndrome | 0.6 | 0.6 | 0.6 | 0.6 | 1.1 | 0.6 |
| History of Crohn disease | 0.4 | 0.3 | 0.4 | 0.4 | 1.1 | 0.4 |
| History of diverticulitis or diverticulosis | 1.1 | 0.8 | 1.1 | 1.1 | 1.7 | 1.2 |
| History of myocardial infarction | 1.2 | 0.8 | 1.2 | 1.2 | 1.9 | 1.3 |
| History of congestive heart failure | 1.8 | 1.4 | 1.8 | 1.8 | 4.1 | 1.9 |
| Peripheral vascular disease | 1.0 | 0.8 | 1.0 | 1.0 | 2.5 | 1.1 |
| Cerebrovascular accident | 1.3 | 1.1 | 1.4 | 1.3 | 2.4 | 1.5 |
| Transient ischemic attack | 0.3 | 0.3 | 0.3 | 0.3 | 0.7 | 0.4 |
| Dementia | 1.5 | 1.2 | 1.5 | 1.5 | 2.7 | 1.6 |
| Chronic obstructive pulmonary disease | 4.4 | 3.3 | 4.4 | 4.4 | 10.0 | 4.5 |

| Characteristic (%) | New users versus nonusers | | | New users versus prevalent users | | |
|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 591,180 | Nonusers N = 7,812,690 | Nonusers N = 591,234 | New users N = 591,180 | Prevalent users N = 270,103 | Prevalent users N = 587,597 |
| Peptic ulcer disease | 0.7 | 0.6 | 0.7 | 0.7 | 1.6 | 0.7 |
| Liver disease | 0.5 | 0.3 | 0.5 | 0.5 | 1.1 | 0.5 |
| Diabetes mellitus | 9.7 | 7.4 | 9.7 | 9.7 | 16.2 | 10.1 |
| Hemiplegia | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 |
| Chronic kidney disease | 1.4 | 1.1 | 1.4 | 1.4 | 2.9 | 1.6 |
| Current tumour | 4.4 | 3.6 | 4.4 | 4.4 | 8.4 | 4.7 |
| **Subclass of indication** | | | | | | |
| Dislocations, sprains, and strains | 37.5 | 43.4 | 37.5 | 37.5 | 43.6 | 37.6 |
| Fracture and major trauma | 35.5 | 8.6 | 35.5 | 35.5 | 21.6 | 35.4 |
| Burns and wounds | 14.4 | 35.3 | 14.4 | 14.4 | 22.5 | 14.4 |
| Other trauma | 12.6 | 12.7 | 12.6 | 12.6 | 12.4 | 12.6 |

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]Alberta data were available as of 2008 and Ontario as of 2013.

[b]Site-specific definition; missing values not reported and account for discrepancies between income quintile categories and overall cohort totals. Data not reported for British Columbia, which was able to adjust for low income versus not low income (or missing) rather than quintiles.

## Table 34: Baseline Characteristics of Opioids New Users, Nonusers, and Prevalent Users Before and After IPTW Weighting for the Trauma Indication Cohort

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 223,181 | Nonusers N = 2,746,394 | Prevalent users N = 92,378 | New users N = 3,059,190 | Nonusers N = 3,062,320 | Prevalent users N = 2,981,891 |
| **Calendar year of cohort entry[a]** | | | | | | |
| 2004 to 2007 | 17.4 | 17.1 | 23.9 | 17.5 | 17.3 | 16.9 |
| 2008 to 2011 | 12.2 | 10.2 | 15.3 | 10.5 | 10.5 | 10.9 |
| 2012 to 2015 | 36.0 | 32.7 | 32.0 | 33.0 | 32.9 | 33.6 |
| 2016 to 2020 | 34.4 | 40.1 | 28.8 | 39.0 | 39.3 | 38.6 |
| **Site** | | | | | | |
| Manitoba | 26.1 | 21.2 | 40.4 | 22.2 | 22.2 | 22.4 |
| Ontario | 53.3 | 57.8 | 41.2 | 56.9 | 57.0 | 56.9 |
| Saskatchewan | 20.5 | 21.0 | 18.4 | 20.9 | 20.9 | 20.7 |
| **Age (years)** | | | | | | |
| 18 to 39 | 31.3 | 38.9 | 19.8 | 37.4 | 37.8 | 37.0 |
| 40 to 64 | 44.4 | 42.0 | 47.3 | 42.1 | 42.3 | 41.3 |
| 65 to 79 | 16.8 | 13.5 | 20.9 | 14.2 | 14.0 | 14.4 |
| 80+ | 7.6 | 5.6 | 11.9 | 6.3 | 6.0 | 7.2 |
| **Sex** | | | | | | |
| Males | 51.4 | 47.0 | 45.8 | 47.2 | 47.3 | 47.7 |
| Females | 48.6 | 53.0 | 54.2 | 52.8 | 52.7 | 52.3 |
| **Income quintile[b]** | | | | | | |
| First (lowest) | 21.3 | 19.2 | 28.7 | 19.5 | 19.6 | 20.3 |
| Second | 19.6 | 19.1 | 20.1 | 19.1 | 19.2 | 19.4 |

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 223,181 | Nonusers N = 2,746,394 | Prevalent users N = 92,378 | New users N = 3,059,190 | Nonusers N = 3,062,320 | Prevalent users N = 2,981,891 |
| Third | 18.7 | 18.9 | 17.0 | 18.8 | 18.8 | 19.0 |
| Fourth | 17.7 | 18.5 | 14.6 | 18.3 | 18.3 | 17.8 |
| Fifth (highest) | 16.6 | 18.2 | 12.1 | 17.9 | 17.9 | 17.2 |
| **Comorbidities** | | | | | | |
| History of irritable bowel syndrome | 0.9 | 0.9 | 1.6 | 0.9 | 0.9 | 1.0 |
| History of Crohn disease | 0.4 | 0.3 | 1.0 | 0.3 | 0.3 | 0.4 |
| History of diverticulitis or diverticulosis | 1.4 | 1.0 | 2.1 | 1.1 | 1.0 | 1.2 |
| History of myocardial infarction | 2.3 | 1.5 | 3.4 | 1.7 | 1.7 | 2.0 |
| History of congestive heart failure | 2.1 | 1.4 | 4.9 | 1.6 | 1.5 | 2.0 |
| Peripheral vascular disease | 1.0 | 0.6 | 2.8 | 0.8 | 0.7 | 0.9 |
| Cerebrovascular accident | 1.7 | 1.2 | 3.0 | 1.4 | 1.3 | 1.6 |
| Transient ischemic attack | 0.3 | 0.2 | 0.6 | 0.3 | 0.2 | 0.3 |
| Dementia | 2.0 | 1.2 | 3.4 | 1.4 | 1.3 | 1.7 |
| Chronic obstructive pulmonary disease | 4.6 | 3.2 | 10.8 | 3.7 | 3.5 | 3.9 |
| Peptic ulcer disease | 0.7 | 0.5 | 1.7 | 0.6 | 0.6 | 0.7 |
| Liver disease | 0.5 | 0.3 | 1.0 | 0.3 | 0.3 | 0.4 |

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 223,181 | Nonusers N = 2,746,394 | Prevalent users N = 92,378 | New users N = 3,059,190 | Nonusers N = 3,062,320 | Prevalent users N = 2,981,891 |
| Diabetes mellitus | 11.5 | 8.3 | 19.3 | 9.0 | 8.9 | 9.7 |
| Hemiplegia | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 |
| Chronic kidney disease | 1.7 | 1.0 | 3.5 | 1.2 | 1.2 | 1.5 |
| Current tumour | 5.2 | 4.0 | 10.1 | 4.4 | 4.3 | 4.9 |
| **Subclass of indication** | | | | | | |
| Dislocations, sprains, and strains | 32.9 | 39.1 | 36.9 | 38.6 | 38.6 | 39.0 |
| Fracture and major trauma | 37.4 | 8.4 | 22.6 | 10.9 | 10.9 | 11.0 |
| Burns and wounds | 16.5 | 39.7 | 27.2 | 37.6 | 37.6 | 37.1 |
| Other trauma | 13.2 | 12.8 | 13.3 | 12.9 | 12.9 | 12.9 |

IPTW = inverse probability of treatment weighting.

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]Ontario data were available as of 2013.

[b]Site-specific definition; missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

## Table 35: Baseline Characteristics of Opioids New Users, Nonusers, and Prevalent Users Before and After Odds Weighting for the Other Pain Indication Cohort

| Characteristic (%) | New users versus nonusers | | | New users versus prevalent users | | |
|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 305,797 | Nonusers N = 5,245,440 | Nonusers N = 305,895 | New users N = 305,797 | Prevalent users N = 212,504 | Prevalent users N = 305,025 |
| **Calendar year of cohort entry[a]** | | | | | | |
| 2004 to 2007 | 5.3 | 7.1 | 5.3 | 5.3 | 8.4 | 5.1 |
| 2008 to 2011 | 20.4 | 30.5 | 20.4 | 20.4 | 32.2 | 20.5 |
| 2012 to 2015 | 36.3 | 30.1 | 36.4 | 36.3 | 31.0 | 36.2 |
| 2016 to 2020 | 38.0 | 32.4 | 38.0 | 38.0 | 28.4 | 38.2 |
| **Site** | | | | | | |
| Alberta | 32.9 | 51.0 | 32.9 | 32.9 | 43.5 | 33.0 |
| Manitoba | 7.9 | 10.5 | 7.9 | 7.9 | 14.0 | 7.9 |
| Ontario | 51.5 | 28.3 | 51.5 | 51.5 | 33.8 | 51.4 |
| Saskatchewan | 7.7 | 10.2 | 7.7 | 7.7 | 8.7 | 7.7 |
| **Age (years)** | | | | | | |
| 18 to 39 | 32.1 | 44.6 | 32.1 | 32.1 | 20.4 | 31.9 |
| 40 to 64 | 44.1 | 37.8 | 44.1 | 44.1 | 50.6 | 43.8 |
| 65 to 79 | 17.4 | 12.4 | 17.4 | 17.4 | 20.1 | 17.6 |
| 80+ | 6.4 | 5.2 | 6.5 | 6.4 | 8.9 | 6.7 |
| **Sex** | | | | | | |
| Males | 50.7 | 44.0 | 50.7 | 50.7 | 49.9 | 51.2 |
| Females | 49.3 | 56.0 | 49.3 | 49.3 | 50.1 | 48.8 |

| Characteristic (%) | New users versus nonusers | | | New users versus prevalent users | | |
|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 305,797 | Nonusers N = 5,245,440 | Nonusers N = 305,895 | New users N = 305,797 | Prevalent users N = 212,504 | Prevalent users N = 305,025 |
| **Income quintile[b]** | | | | | | |
| First (lowest) | 21.0 | 20.9 | 21.0 | 21.0 | 28.6 | 21.1 |
| Second | 20.0 | 20.0 | 20.0 | 20.0 | 20.5 | 20.0 |
| Third | 18.9 | 18.5 | 18.9 | 18.9 | 16.9 | 19.0 |
| Fourth | 17.8 | 17.3 | 17.8 | 17.8 | 14.6 | 17.7 |
| Fifth (highest) | 17.1 | 17.1 | 17.1 | 17.1 | 12.9 | 17.1 |
| **Comorbidities** | | | | | | |
| History of irritable bowel syndrome | 1.3 | 0.8 | 1.3 | 1.3 | 1.8 | 1.3 |
| History of Crohn disease | 0.6 | 0.3 | 0.6 | 0.6 | 1.1 | 0.6 |
| History of diverticulitis or diverticulosis | 1.5 | 0.9 | 1.6 | 1.5 | 2.0 | 1.6 |
| History of myocardial infarction | 2.7 | 1.3 | 2.7 | 2.7 | 3.1 | 2.8 |
| History of congestive heart failure | 2.0 | 1.4 | 2.0 | 2.0 | 4.1 | 2.1 |
| Peripheral vascular disease | 1.2 | 0.7 | 1.2 | 1.2 | 2.3 | 1.2 |
| Cerebrovascular accident | 1.8 | 1.6 | 1.8 | 1.8 | 2.8 | 1.9 |
| Transient ischemic attack | 0.4 | 0.5 | 0.4 | 0.4 | 0.6 | 0.4 |
| Dementia | 1.2 | 1.2 | 1.2 | 1.2 | 2.4 | 1.3 |

| Characteristic (%) | New users versus nonusers | | | New users versus prevalent users | | |
|---|---|---|---|---|---|---|
| | Unweighted | | Odds weighted | Unweighted | | Odds weighted |
| | New users N = 305,797 | Nonusers N = 5,245,440 | Nonusers N = 305,895 | New users N = 305,797 | Prevalent users N = 212,504 | Prevalent users N = 305,025 |
| Chronic obstructive pulmonary disease | 4.4 | 3.2 | 4.5 | 4.4 | 10.0 | 4.5 |
| Peptic ulcer disease | 0.8 | 0.6 | 0.8 | 0.8 | 1.7 | 0.9 |
| Liver disease | 0.5 | 0.3 | 0.5 | 0.5 | 1.1 | 0.5 |
| Diabetes mellitus | 12.3 | 7.6 | 12.4 | 12.3 | 17.7 | 12.5 |
| Hemiplegia | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 |
| Chronic kidney disease | 2.0 | 1.1 | 2.0 | 2.0 | 3.2 | 2.1 |
| Current tumour | 8.3 | 3.8 | 8.3 | 8.3 | 10.9 | 8.5 |
| **Subclass of indication** | | | | | | |
| Nephrolithiasis or cholecystitis | 12.9 | 3.1 | 12.9 | 12.9 | 7.5 | 13.0 |
| Headache and migraine | 49.3 | 83.6 | 49.3 | 49.3 | 70.9 | 49.4 |
| Nonsurgical deliveries | 5.3 | 8.0 | 5.3 | 5.3 | 0.9 | 5.3 |
| Back pain | 32.4 | 5.3 | 32.4 | 32.4 | 20.8 | 32.4 |

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]Alberta data were available as of 2008 and Ontario as of 2013.

[b]Site-specific definition; missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

## Table 36: Baseline Characteristics of Opioids New Users, Nonusers, and Prevalent Users Before and After IPTW Weighting for the Other Pain Indication Cohort

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 205,177 | Nonusers N = 2,567,890 | Prevalent users N = 120,011 | New users N = 2,888,869 | Nonusers N = 2,893,001 | Prevalent users N = 2,851,016 |
| **Calendar year of cohort entry[a]** | | | | | | |
| 2004 to 2007 | 7.8 | 14.5 | 14.9 | 14.2 | 14.1 | 13.9 |
| 2008 to 2011 | 5.6 | 9.6 | 10.4 | 9.4 | 9.4 | 9.6 |
| 2012 to 2015 | 39.8 | 31.4 | 35.7 | 32.5 | 32.2 | 32.5 |
| 2016 to 2020 | 46.7 | 44.4 | 39.0 | 44.0 | 44.4 | 44.1 |
| **Site** | | | | | | |
| Manitoba | 11.8 | 21.5 | 24.7 | 21.0 | 20.9 | 21.0 |
| Ontario | 76.7 | 57.8 | 59.8 | 59.2 | 59.2 | 59.3 |
| Saskatchewan | 11.5 | 20.8 | 15.5 | 19.8 | 19.9 | 19.7 |
| **Age (years)** | | | | | | |
| 18 to 39 | 30.4 | 42.2 | 17.9 | 40.2 | 40.3 | 39.2 |
| 40 to 64 | 44.3 | 37.0 | 48.8 | 37.8 | 38.0 | 37.2 |
| 65 to 79 | 18.3 | 14.5 | 22.6 | 15.3 | 15.1 | 15.7 |
| 80+ | 6.9 | 6.3 | 10.7 | 6.8 | 6.6 | 7.9 |
| **Sex** | | | | | | |
| Males | 52.0 | 42.0 | 51.3 | 43.0 | 43.1 | 44.4 |
| Females | 48.0 | 58.0 | 48.7 | 57.0 | 56.9 | 55.6 |
| **Income quintile[b]** | | | | | | |
| First (lowest) | 19.2 | 17.9 | 25.6 | 18.3 | 18.3 | 18.4 |
| Second | 19.0 | 17.9 | 19.2 | 18.1 | 18.0 | 18.0 |

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 205,177 | Nonusers N = 2,567,890 | Prevalent users N = 120,011 | New users N = 2,888,869 | Nonusers N = 2,893,001 | Prevalent users N = 2,851,016 |
| Third | 18.8 | 17.8 | 16.6 | 17.8 | 17.8 | 18.1 |
| Fourth | 18.2 | 17.4 | 14.7 | 17.4 | 17.4 | 17.2 |
| Fifth (highest) | 17.4 | 16.9 | 12.9 | 16.7 | 16.8 | 16.5 |
| **Comorbidities** | | | | | | |
| History of irritable bowel syndrome | 1.6 | 1.1 | 2.3 | 1.2 | 1.2 | 1.3 |
| History of Crohn disease | 0.5 | 0.3 | 1.0 | 0.4 | 0.4 | 0.4 |
| History of diverticulitis or diverticulosis | 1.7 | 1.2 | 2.3 | 1.3 | 1.3 | 1.4 |
| History of myocardial infarction | 3.5 | 2.0 | 4.5 | 2.3 | 2.3 | 2.5 |
| History of congestive heart failure | 2.0 | 1.7 | 4.7 | 1.9 | 1.8 | 2.2 |
| Peripheral vascular disease | 1.0 | 0.7 | 2.5 | 0.9 | 0.8 | 0.9 |
| Cerebrovascular accident | 1.8 | 2.2 | 3.4 | 2.3 | 2.2 | 2.6 |
| Transient ischemic attack | 0.3 | 0.5 | 0.6 | 0.5 | 0.5 | 0.5 |
| Dementia | 1.3 | 1.3 | 2.9 | 1.4 | 1.4 | 1.6 |
| Chronic obstructive pulmonary disease | 4.2 | 3.6 | 10.3 | 4.0 | 4.0 | 4.2 |
| Peptic ulcer disease | 0.8 | 0.6 | 1.7 | 0.7 | 0.7 | 0.8 |
| Liver disease | 0.4 | 0.3 | 1.1 | 0.4 | 0.4 | 0.4 |

| Characteristic (%) | Unweighted | | | IPTW weighted | | |
|---|---|---|---|---|---|---|
| | New users N = 205,177 | Nonusers N = 2,567,890 | Prevalent users N = 120,011 | New users N = 2,888,869 | Nonusers N = 2,893,001 | Prevalent users N = 2,851,016 |
| Diabetes mellitus | 13.2 | 9.1 | 19.6 | 10.0 | 9.9 | 10.4 |
| Hemiplegia | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 | 0.1 |
| Chronic kidney disease | 2.1 | 1.2 | 3.7 | 1.5 | 1.4 | 1.6 |
| Current tumour | 8.6 | 4.7 | 12.6 | 5.4 | 5.3 | 5.8 |
| **Subclass of indication** | | | | | | |
| Nephrolithiasis or cholecystitis | 16.3 | 4.5 | 10.6 | 5.6 | 5.6 | 5.7 |
| Headache and migraine | 36.0 | 77.3 | 62.6 | 73.8 | 73.7 | 73.6 |
| Nonsurgical deliveries | 6.1 | 11.2 | 0.9 | 10.4 | 10.4 | 10.5 |
| Back pain | 41.5 | 7.0 | 25.8 | 10.2 | 10.2 | 10.3 |

IPTW = inverse probability of treatment weighting.

Notes: Data presented as percentage.

Percentages may not add up to 100% due to rounding.

[a]Ontario data were available as of 2013.

[b]Site-specific definition; missing values not reported and account for discrepancies between income quintile categories and overall cohort totals.

## Table 37: Crude Incidence Rates of Diverticulitis Among New Users by Outcome Definition and Follow-up for the Trauma and Other Pain Indications, by Region

| Outcome and follow-up | Trauma indication | | | Other pain indication | | |
|---|---|---|---|---|---|---|
| | Total person-years | Total events | Crude incidence rate (per 10,000 person-years) | Total person-years | Total events | Crude incidence rate (per 10,000 person-years) |
| **Outcome 1, intention to treat** | | | | | | |
| **Canada** | **2,619,323** | **6,879** | **26.3** | **1,938,639** | **6,137** | **31.7** |
| Alberta | 1,013,010 | 2,719 | 26.8 | 689,689 | 2,334 | 33.8 |
| Manitoba | 590,718 | 1,499 | 25.4 | 250,354 | 690 | 27.6 |
| Ontario | 649,930 | 1,263 | 19.4 | 834,749 | 2,371 | 28.4 |
| Saskatchewan | 365,665 | 1,398 | 38.2 | 163,847 | 742 | 45.3 |
| **Outcome 1, as treated** | | | | | | |
| **Canada** | **47,248** | **121** | **25.6** | **40,684** | **157** | **38.6** |
| Alberta | 6,702 | 12 | 17.9 | 15,349 | 56 | 36.5 |
| Manitoba | 5,555 | 21 | 37.8 | 3,141 | 8 | 25.5 |
| Ontario | 8,805 | 26 | 29.5 | 11,584 | 50 | 43.2 |
| Saskatchewan | 26,185 | 62 | 23.7 | 10,609 | 43 | 40.5 |
| **Outcome 2, intention to treat** | | | | | | |
| **Canada** | **4,198,129** | **1,276** | **3.0** | **1,774,793** | **845** | **4.8** |
| Alberta | 1,013,010 | 322 | 3.2 | 689,689 | 223 | 3.2 |
| British Columbia | 1,944,472 | 340 | 1.7 | NA | NA | NA |
| Manitoba | 590,718 | 318 | 5.4 | 250,354 | 135 | 5.4 |
| Ontario | 649,930 | 296 | 4.6 | 834,749 | 487 | 5.8 |
| **Outcome 2, as treated** | | | | | | |
| **Canada** | **38,012** | **21** | **5.5** | **30,075** | **30** | **10.0** |

| Outcome and follow-up | Trauma indication | | | Other pain indication | | |
|---|---|---|---|---|---|---|
| | Total person-years | Total events | Crude incidence rate (per 10,000 person-years) | Total person-years | Total events | Crude incidence rate (per 10,000 person-years) |
| Alberta | 6,702 | 0 | 0.0 | S | S | 2.6 |
| British Columbia | S | S | 2.4 | NA | NA | NA |
| Manitoba | 5,555 | 8 | 14.4 | S | S | 9.5 |
| Ontario | 8,805 | 10 | 11.4 | 11,584 | 24 | 20.7 |

ED = emergency department; NA = not applicable; S = value suppressed.

Notes: Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT or MRI scan.

Manitoba data were not available for ED visits for outcome 1.

Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

# Appendix 5: Summary of Findings for the Comparative Safety Study

Please note that this appendix has not been copy-edited.

## Table 38: Main Results for the As-Treated and Intention-to-Treat New Users Versus Odds-Weighted Nonusers Analyses by Indication Cohort

| Main analysis and outcome[a] | Postsurgical cohort[b] | | Trauma cohort[c] | | Other pain cohort[d] | |
|---|---|---|---|---|---|---|
| | IRR (95% CI) | IRD per 10,000 person-years (95% CI) | IRR (95% CI) | IRD per 10,000 person-years (95% CI) | IRR (95% CI) | IRD per 10,000 person-years (95% CI) |
| **As-treated odds weighted** | | | | | | |
| Outcome 1 | 1.38 (0.93, 2.04) | 7.97 (−2.98, 18.92) | 1.61 (0.99, 2.64) | 9.73 (−1.79, 21.25) | 1.61 (1.10, 2.35) | 12.49 (2.81, 22.17) |
| Outcome 2 | 2.40 (1.76, 3.28) | 3.36 (1.19, 5.54) | 3.96 (2.44, 6.43) | 5.78 (−0.64, 12.19) | 4.38 (2.44, 7.85) | 11.08 (0.38, 21.79) |
| **Intention-to-treat odds weighted** | | | | | | |
| Outcome 1 | 1.08 (1.03, 1.14) | 3.10 (0.59, 5.62) | 1.10 (1.03, 1.19) | 2.42 (0.64, 4.21) | 1.07 (0.95, 1.20) | 1.92 (−1.54, 5.39) |
| Outcome 2 | 1.00 (0.95, 1.05) | −0.04 (−0.19, 0.10) | 1.21 (1.12, 1.31) | 0.53 (0.22, 0.84) | 1.09 (1.00, 1.18) | 0.37 (−0.01, 0.74) |

CI = confidence interval; CPRD = Clinical Practice Research Datalink; IRD = incidence rate difference; IRR = incidence rate ratio.

[a]Outcome 1 is ED or inpatient visit for diverticulitis and outcome 2 is inpatient visit for diverticulitis with a CT scan. Data not available for British Columbia and US Merative MarketScan for outcome 1, and for Saskatchewan for outcome 2.

[b]Data for the postsurgical cohort includes Alberta, British Columbia, Manitoba, Ontario, Saskatchewan, the UK CPRD, and the US Merative MarketScan.

[c]Data for the trauma cohorts includes Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan.

[d]Data for the other pain cohort includes Alberta, Manitoba, Ontario, and Saskatchewan.

For more information on CoLab and its work, visit [colab.cda-amc.ca](colab.cda-amc.ca).

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CDA-AMC is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with the Post-Market Drug Evaluation Program to produce credible and timely evidence on postmarket drug safety and effectiveness.