Study Protocol:

Persistent opioid use and opioid-related harm after hospital admissions for surgery and trauma in New Zealand: A Population-based Cohort Study

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# Background:

Opioids are widely prescribed in hospitals for acute, chronic non-cancer and cancer-related pain. However, in the last decade, opioid addiction and dependency have contributed substantially towards hospitalisation and death globally, especially in the United States (US).1 Mortality related to opioid overdose accounts for nearly 530 deaths per week in the US.1 In New Zealand (NZ), a study in 2017 showed from 2008 to 2012, a total of 325 deaths were primarily ascribed to opioid use.2 Of these, 179 deaths were from unintentional overdose and may be preventable.2 No studies have examined recent trends in NZ. In NZ, five strong opioids and a total of 33 different formulations are licensed for prescribing in pain management: 14 for morphine, 9 for oxycodone, 5 for fentanyl, 4 for methadone and 1 for pethidine. Three weak opioids and a total of 9 different formulations are available for prescribing: 5 for tramadol, 3 for codeine and 1 for dihydrocodeine.

The NZ Health Quality & Safety Commission (HQSC) in 20163 reports that opioid use has increased in NZ with 16.6 per 1000 people compared to 14.4 per 1000 in 2011. The rate of persistent opioid use, defined by the HQSC as use of six weeks or longer, has not changed between 2011 to 2016 and is around 2 per 1000 patients. The report also showed that almost half of the patients dispensed a strong opioid had a hospital admission in the week prior to opioid prescribing in the community.

Internationally, persistent opioid use is generally defined as opioid use for 90 days or longer.4 Studies from the US and Canada have indicated the rate of persistent opioid use beyond 90 days to be between 0.1% to 8.2% in the context of pain management after surgery and trauma.5 In the acute setting, higher rates of opioid prescribing by emergency physicians has also been linked to subsequent long-term opioid use in the US (Odds Ratio (OR) 1.30,95% CI 1.23, 1.37, p<0.001).6

Hospital admissions may act as drivers for subsequent persistent opioid use in the community setting. NZ data shows that younger people (under 24 years of age) were more likely to have a hospital admission prior to the dispensing of a strong opioid than older people (80 years and over)– rates opioid dispensing were 7 per 10 people in younger people vs 3.7 per 10 in those above 80.3 This usage rate may be due to clinicians' perception that opioids are generally safer in younger patients because they are more likely to have normal metabolic functions. However, studies have suggested that addictive behaviour tends to be overrepresented in younger patients (18 to 29 years old),7 8 mainly concerning other substances of abuse such as cannabis and cocaine. Our study will examine persistent opioid use and opioid-related harm across all age groups, to describe how these rates may change across ages.

Outcomes related to persistent opioid use have also been poorly evaluated both in NZ and elsewhere. A recent study published by a Swedish group showed that post-trauma patients with persistent opioid use carry an excess risk of mortality, even after adjustment for age, sex, somatic comorbidity, psychiatric-morbidity, substance abuse, injury severity and admissions to intensive care (Hazard Ratio (HR) 1.82, 95% CI 1.34, 2.48, p<0.001).9 There are few mortality data in NZ related to persistent opioid use, despite the presence of national databases recording health outcomes.

In NZ, the opportunity for population-based cohort studies is unique in several ways. Firstly, NZ has a single universal healthcare system; the government covers 80% of the cost of healthcare. All NZ citizens, permanent residents, and certain work visa holders have access to free or low-cost physician services, hospital care, and prescription medicines.10 Physician services are private businesses that set their consultation fee, but the fees are set by the government and cannot exceed a certain limit. Patients enrolled in a specific physician service will have a lower cost per visit, as the government would partially fund the visit.10 Most physician services are free for patients 13 years or under. Most prescription medicines are fully funded by the government, with the patient having to co-pay only a dispensing fee of NZ$5 per item to the pharmacy.11 Secondly, all patients accessing the health and disability system will be assigned a unique identifier code, in both private and public funded hospitals, called the National Health Index (NHI) number.12 The Ministry of Health (MOH) uses the NHI number in an encrypted form so that data can be used for statistical purposes to report on the health of the NZ population.12 This then allows for linkage of data across different datasets for research, e.g. hospital admissions, medication dispensing, and mortality can be linked. Thirdly, it is possible to track all admissions to public and private hospitals. This permits the calculation of an emerging measure called Days Alive and Out of Hospital (DAOH). DAOH is a composite outcome that integrates several clinically significant outcomes, including mortality, hospital length-of-stay, and hospital readmission.13 It is sensitive to any complication of surgery that prolongs an admission, leads to a readmission or results in death. Fourthly, data on ethnicity are routinely collected by the MOH. NZ has a large indigenous population (Māori) who experience substantial disadvantages in health status and outcomes compared with the non-Māori population.14 A recent study assessing the use of non-opioid analgesia between ethnicities in NZ showed a significant disparity in outcome between Māori and non- Māori patients, with Māori patients having more in adverse events, with a relative risk 2.54 (95% CI 2.23-2.90).15 The likely risk of persistent opioid use and subsequent opioid-related harm in NZ may also be distributed unequally across ethnic groups. The NZ healthcare system is obligated to address these inequities under the *protection* principle of the *Treaty of Waitangi.*16

Thus, we aim to determine the patterns of opioid use and opioid-related harm in NZ following discharge from hospital for surgery or trauma over 13 years from 1st of January 2007 to 31st of December 2019. Specifically, in this study, we aim to determine the rates and predictors of persistent opioid use post-discharge from the hospital and evaluate outcomes between persistent and non-persistent opioid users including all-cause mortality, opioid-related mortality, all-cause hospitalisation, opioid-related hospitalisation and DAOH between 180 to 360 days after date of hospital discharge due to surgery or trauma.

# Methods and Analysis:

## Study design and setting

This will be a population-based retrospective cohort study involving residents of NZ using linked, routinely collected health data. We plan to start data collection and analysis by 1st of March 2021 and complete the study within 12 months.

## Sources of data

The study will use several national administrative health databases, which can be linked via an encrypted, unique patient identifier known as the National Health Index (NHI).12 To examine hospitalisations data, we will use the National Minimum Data Set (NMDS).17 The NMDS is a national registry of all inpatient admissions reported to the MOH. The NMDS includes information on dates of hospital stay, diagnoses, and medical procedures. All medical procedures are coded according to the Australasian Classification of Health Interventions (ACHI).18 In NMDS, primary and secondary diagnoses are coded according to the International classification of diseases 10th edition – Australian modified version (ICD‐10AM). The NMDS captures 99 percent of all operations performed in NZ.19 The National Non-Admitted Patients Collection (NNPAC) is the national database used to capture information on patients who presented to the emergency department (ED) and spent less than three hours in a hospital. The Mortality Collection (MORT) is a national database that classifies the underlying cause of death for all deaths registered in NZ. MORT uses the ICD-10AM classification for mortality coding.20 Mortality related outcomes and cause of deaths will be retrieved from this database.

Data on opioid dispensing and other medicines prescribed to patients receiving opioids will be obtained from the Pharmaceutical Collection (Pharms). Pharms is a data warehouse of information related to pharmaceutical subsidies and contains claim and payment information from pharmacists for subsidised dispensing.21 Medicines dispensed in hospitals are not included in the database. Patients meeting the inclusion criteria will be determined from the NMDS then matched with their respective opioid dispensing data from Pharms via their respective encrypted NHI.

Other databases that we will access include the NHI and Primary Health Organisation (PHO) enrolment. These datasets will be used to retrieve information relevant to the patient, including demographic, gender, age, ethnicity, and social-economic status.22

## Study Cohort

The study cohort selection is illustrated in Figure 1.The study population includes all opioid-naïve patients (of any age) who had a surgical procedure or presented to the hospital with trauma in one of NZ's 39 public hospitals between the 1st of January 2007 to 31st of December 2019. Surgical patients will be defined as all individuals in the NMDS assigned a surgical procedure and associated anaesthetic code via the ACHI. Trauma patients with a hospital stay of greater than three hours will be identified using ICD-10AM codes for trauma in the NMDS dataset. database.

The date of hospital discharge following the initial surgical or traumatic event and exposed to opioids will be considered as the index date. For patients with more than one admission for surgical procedures or trauma during the study period, only the first admission during the study period will be included in the study cohort. In the surgical cohort, those with concomitant trauma diagnosis will also be excluded and will be analysed separately as part of the trauma cohort.

Only patients who were dispensed any opioids within a seven-day period (day 0 being the index date) after hospital discharge following the surgical or traumatic event were included. We only included opioid-naïve patients and to be considered as opioid-naïve, we excluded the following types of patients: 1) those with evidence of opioid use disorders (e.g. overdose, misuse or dependence) in the 365 days prior to the index date; 2) those with any community pharmacy dispensing of opioid prescriptions in the 180 days prior to the index date.

For the analysis of the primary outcome analysis, in addition to the exclusion criteria above, patients who died during the follow-up period (365 days from index date) will be excluded as per previous studies.23-27 Trauma patients who have recurrent trauma, or surgical patients who have recurrent surgery, during the 365 days of follow up will also be excluded.

For the analysis of the secondary outcome analysis, in addition to the exclusion mentioned previously, we will exclude patients who died within the first 180 days after index date as per previous studies.9 28 29

Postoperative prescribing of opioids is generally guided by the Australian and New Zealand College of Anaesthetists (ANZCA) guidelines.30 Multimodal analgesia is utilised instead of mainly opioid-based analgesia to improve pain control and reduce opioid consumption and adverse effects.30

*See supplementary section for surgical procedures and ICD-10AM codes for trauma-related admissions.*

Figure 1. Cohort selection

## Outcome Assessment

### Primary outcome assessment

The primary outcome will be persistent use of opioids after trauma or surgery. As in previous studies of opioid use,31 32 persistent opioid use will be defined as any pharmacy claims for one or more opioid prescription between 91 days to 365 days after the index date. This definition was adapted from recent surgical consensus and meta-analysis of persistent opioid use definitions.33 34 risk factors of persistent and non-persistent opioid users will be compared to identify predictors of persistent opioid use.

### Secondary outcome assessment

The secondary outcomes will be aimed at determining if differences in mortality or morbidity exist between persistent and non-persistent users. The assessment window for persistent opioid use will be shortened from 91-365 days to 91-180 days from the index date to allow comparison of secondary outcomes as in other studies.9 28 29 Patients will be followed up for 180 days after being determined as persistent or non-persistent opioid users to assess if differences in outcomes exist.

The following outcomes will be assessed from 180 days after the index date (i.e., outcomes will be assessed from 180 to 360 days after discharge from either surgical/trauma event): all-cause mortality, opioid-related mortality, all-cause hospitalisation, opioid-related hospitalisation and DAOH. If the primary cause of deaths contained any of the following ICD-10AM codes: F11, F13, F19 T400-T406, X62, Y12, X42, we would consider the cause of deaths to be opioid-related.

## Modifiable risk factors

The main modifiable risk factors of interest were those related to the initial opioid prescription characteristics. We included all opioids available in NZ for pain management in the community, including codeine, tramadol, dihydrocodeine, morphine, oxycodone, fentanyl, methadone, and pethidine. We calculated the total oral morphine equivalence (OME) in milligrams of the opioids dispensed for each patient from the initial prescription, as per our protocol.12 We recorded the types of opioids, whether a slow-release opioid preparation was dispensed and whether switching of opioid type occurred in the first 90 days after the first dispensing. We also collected data on non-opioid analgesics dispensed within this period, such as paracetamol and non-steroidal anti-inflammatory drugs.

## Other non-modifiable risk factors

Other potential risk factors for POU were identified based on the research team experience and previously published literature. These included age, type of surgery, length of stay for the index surgery or trauma event, surgical speciality (cardiac, vascular, digestive, thoracic, neurosurgery, musculoskeletal, urinary and other), multiple surgeries in one day, complexity and urgency of surgery.24-27 37  We will include specific trauma-related variables including if patients underwent surgery during admission and the site(s) of injury. These will be collected via the NMDS in addition to ethnicity, gender, socioeconomic status, social deprivation score (via NZ Deprivation Index-NZDep 2018).38 The NZDep is an area-based measure of socioeconomic deprivation in New Zealand. Ethnicity data in NZ is prioritised in the following order: Māori, Pacific, Asian, other ethnic groups, and European. The urgency of the surgery will be categorised as elective or acute. The operative complexity will be categorised using the Johns Hopkins five-category classification, where each procedure will be given an operation severity grade from one to five.39 The method of identifying all procedures performed in NZ hospitals is consistent with a previously published paper involving current co-investigators on postoperative mortality risk.19

Other comorbidities will be collected 365 days before the index date as they have been shown in the literature to be predictors of persistent opioid use5 24 40 such as depression (ICD-10AM codes: F32 -F33), anxiety (F40-F48), dementia (F00-F03), schizophrenia and related psychotic conditions (F20-F29), bipolar disorder (F31), alcohol and nicotine dependence (F10.20- F10.29, F17.200- F17.299), substance use (F10-F16, F18-F19, F55), mood disorder (F30-F39), other mental health conditions (F04-F09, F51-F53, F59, F63, F68, F69, F930-F932, F99), smoking, cancer and chronic kidney or liver disease, cardiac disorders, respiratory disorders, and diabetes mellitus and chronic pain. For each patient included in the cohort, the M3 index (M3I) score, Charlson comorbidity index41 and the American Society of Anesthesiologists (ASA) physical status classification system42 will be used as a measure of comorbidity using information from any inpatient or outpatient contact up to five years before the index date i.e. For a patient included in 2007, we will have to look back their NMDS data from 2002 to calculate their comorbidity index.43 M3I score will be computed from a list of 61 health conditions based on the presence/absence of previous diagnostic codes (see the supplementary section for the specific health conditions). We will use the ASA score on each patient’s NMDS record at the time of surgery. Additionally, we will adjust for the year of cohort entry in multivariable models assessing the relationship between explanatory variables and outcomes of interest.

To assess concurrent medications use, we will examine patient's medications at baseline by searching a period of 365 days before the index date using the Pharms database. Concomitant medications that are potential predictors for persistent opioid use include non-opioid analgesia, including paracetamol, pregabalin, gabapentin, benzodiazepines, antipsychotics, mood stabilisers and antidepressants. Additionally, information on non-steroidal anti-inflammatories (NSAIDs) dispensing will be collected as these have been shown to predict persistent opioid use.36 44

## Data analysis

Descriptive statistics will be used to describe baseline characteristics and the outcomes of interest. Continuous variables will be described using the mean and standard deviation or median and interquartile range as appropriate, depending on data distribution. Categorical variables will be described using frequency distributions and percentages. Kolmogorov–Smirnov and Shapiro-Wilk tests of normality will be used to assess the distribution of continuous variables. Parametric and non-parametric bivariate tests (e.g. Student's t-test, Mann-Whitney U test or χ2 test) will be used to compare the characteristics of individuals who may or may not exhibit persistent opioid use after surgery or trauma.

A multivariable logistic regression model will be used to examine the association between potential predictors and persistent opioid use after surgery/trauma. Forward and backward conditional models will be used to minimise multicollinearity. Adjusted odds ratios (aOR) with 95% confidence intervals (95% CI) will be reported for modifiable risk factors and ethnicity. We used the Wald test, adjusted by the degree of freedom, to assess the relative effect size of the non-modifiable risk factors in the multivariable analysis and reported the aOR and 95% CI of the ten risk factors with the largest effect size45 Quantile regression will be used to assess differences in DAOH between persistent and non-persistent opioid users, adjusted for relevant risk factors. The particular percentile used will 1% (0.01) to 10.0% (0.1) of both surgical or trauma cohort.

We will calculate the crude rate of each outcome of interest for both persistent and non-persistent opioid user groups. To compute the rates, we will divide the total number of outcome events by total follow-up time. These will be reported as cases per 1000 person-days with confidence intervals derived from a Poisson or negative binomial distribution as appropriate. Cox multivariable regression models will be used to estimate the risk of all-cause mortality, opioid-related mortality, all-cause hospitalisation, and opioid-related hospitalisation associated with persistent use of opioids in the 180 to 360 days after the index date for all patients. Hazard ratios and 95% confidence intervals will be reported. The proportional hazards assumption of the Cox model will be tested using a regression strategy where the covariates from the final model are entered first and then following up that model by adding the relevant interaction terms between the time measure and the covariates. We will also visually inspect the Kaplan-Meier (KM) curves of relevant covariates from the regression strategy. A two-sided p-value < 0.05 will be considered statistically significant for all statistical tests. We will undertake all analyses using SPSS v29 IBM corporation, Armonk NY, USA

## Subgroup analysis

We will repeat the primary analyses by stratifying across three age groups (<30, 30-64, ≥65 years) to examine whether the strength of the predictors for persistent opioid use and secondary outcomes vary across age. We will also assess whether the findings of the primary analysis are consistent across subgroups defined according to ethnicity (Māori vs non- Māori), different opioid (Strong, Weak and Multiple),

## Sensitivity analysis

### Primary outcome sensitivity analysis

Three sensitivity analyses will be used to assess the impact of altering the outcome definition and cohort selection criteria on the rate and predictors of persistent opioid use. 1) We will extend the prior opioid use wash out period from 180 days to 365 days. 2) We used a definition of persistent opioid use of any dispensing between 91-180 days. 3) We added a continuity requirement between opioid dispensing to our definition of persistent opioid use (any opioid dispensing between 91-365 days) by allowing no less than 45 days between each opioid dispensing from the initial prescription date.

We undertook an additional sensitivity analysis using the method of the primary analysis with ethnicity as a binary variable, comparing Māori to all other groups (non-Māori) to explore potential health inequities*.*

### Secondary outcome sensitivity analysis

One sensitivity analysis will be used to assess the impact of altering the follow up period for all-cause mortality. 1) We will extend the follow up period for all-cause mortality from 180 days to 365 days.

## Supplementary analysis

The following analyses were included with respect to each outcome to contextualise the primary findings and address limitations in pharmacoepidemiological studies- see figure 2 for flow diagram on patient selection.

### Primary outcome

For comparison to the primary analysis, we will separately count those patients who had no pharmacy claims for opioids within seven days of index date but did have such claims between 91-365 days.

### Secondary outcome

For comparison to all-cause mortality between persistent and non-persistent opioid use, we will consider patients who had pharmacy claims for opioids within seven days of index date as ‘potential persistent users’ and this will be compared to those who did not have claims for opioids. The risk for all-cause mortality will be assessed from seven to 360 days after discharge.

Figure 2. Cohort selection for supplementary analysis

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