Evaluation of Risk Mitigation Measures for People With Substance Use Disorders to Address the Dual Public Health Crises of COVID-19 and Overdose in British Columbia: A Mixed-Methods Study Protocol.

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Abstract

Background

The COVID-19 pandemic was preceded by an ongoing overdose crisis and linked to escalating drug overdose deaths in British Columbia (BC). At the outset of these dual public health emergencies, the BC government announced interim Risk Mitigation Guidance (RMG) that permitted prescribing medication alternatives to substances, including opioids, alcohol, stimulants, and benzodiazepines, an intervention sometimes referred to as 'Safe Supply'. This protocol outlines the approach for a study of the implementation of RMG and its impacts on COVID-19 infection, drug-related and systemic harms, continuity of care for people with substance use disorder, as well as their behavioural, psychosocial, and well-being outcomes.

Methods

We conduct a parallel mixed-method study that involves both analysis of population-level administrative health data and primary data collection, including a 10-week longitudinal observational study (target n=200), a cross-sectional survey (target n=200), and qualitative interviews (target n=60). We have implemented a participatory approach to this evaluation, partnering with people with lived or living experience of substance use, as well as researchers and public health decision-makers across the province. Linked population-level administrative databases will analyze data from a cohort of BC residents with an indication of substance use disorder between 1996 and 2000. We will conduct a high-dimensional propensity score matching and marginal structural modeling to construct a control group and assess the impact of RMG dispensation receipt on a collaboratively-determined set of primary and secondary outcomes.

Discussion

This study constitutes the first formal evaluation of a province-wide program providing regulated pharmaceutical alternatives to the toxic drug supply. The study features an integrated knowledge translation approach, including communications with people with lived/living experience of substance use and consortium meetings with various stakeholders. Supported by the unique research context in BC, our selected mixed method study design will provide an exceptionally strong evidence base to judge not only the impact of the initial implementation of RMG, but also critical evidence on the implementation of the program, which can be used to adapt its future iterations if deemed successful.

Contribution To The Literature

- Amid North America's ongoing overdose epidemic, novel harm reduction innovations are increasingly warranted and prevalent, including 'Safe Supply' prescribing.
- Current research surrounding the prescription of substances to people who use illicit drugs operates within a treatment paradigm and is inadequate to guide the evaluation and development of less controlled harm reduction approaches in real-world settings.
- This study protocol – the first of its kind to our knowledge – proposes a mixed-methods evaluation of the outcomes and implementation of a novel population-level harm reduction initiative to reduce elevated risks of overdose mortality during the COVID-19 pandemic, incorporating qualitative, quantitative, and participatory engagement approaches.

Background

Like other jurisdictions across the globe, British Columbia (BC) Canada has implemented extensive public health measures to reduce the transmission of SARS-CoV-2 (COVID-19). However, Canada is also facing an escalating overdose epidemic (1–4). The COVID-19 pandemic was preceded by an ongoing public health emergency in BC, called in April 2016 as a result of the rapid rise in overdose deaths. BC reported 1,547 illicit drug overdose deaths in 2018 (5), accounting for over a third of overdose deaths in Canada despite being home to just 12% of Canadian residents.(6) The four-fold increase in overdose deaths since 2012 has largely been attributed to the contamination of the illicit drug supply with fentanyl and fentanyl analogues. The most recent BC Coroner's report detected fentanyl in 87% of all drug-related deaths. Many persons who have died from overdose had sought treatment in the past and returned to using illicit drugs, underlining the need to both strengthen the quality of care and expand the set of options to treat or reduce harm resulting from licit and illicit substance use.(7)

BC declared a public health emergency in April 2016, prompting a coordinated and multi-faceted public health response.(8) This included measures to increase accessibility to opioid agonist treatment (OAT) (9–14) and the expansion of harm reduction services, including drug checking services, naloxone distribution, supervised consumption and overdose prevention. These measures appeared to have resulted in some progress in reducing illicit drug overdose deaths in 2019 where the number of overdose deaths declined to 984. Since March 2020 however there have been notable increases in overdose deaths in BC with over 170 persons dying per month (or 5.6 persons per day) from May 2020-July 2020 (15). First Nations in BC have also experienced an increase in overdose deaths with an overdose death rate 5.6 times that of other residents of BC for the first 5 months of 2020 (ref16).

At the intersection of these dual public health emergencies are a number of challenging issues that increase the risk of drug-related and systemic harms, including heightened risk for overdose due to restrictions in access to medical care, social services and harm reduction services (16, 17), contradictory public health messaging that encourages physical distancing while discouraging using drugs alone (18, 19) and an increasingly toxic illicit drug supply (20–22). People who use substances are at heightened risk for COVID-19 infection due to high rates of compounding comorbidities and exposure to conditions where implementing physical distancing and personal hygiene protocols is challenging (23–25).

Federal and provincial governments have implemented policies to counteract potential secondary effects of the public health response to COVID-19, including allowing pharmacists to renew prescriptions (26), issuing temporary exemptions for OAT prescriptions (27, 28), and increased use and promotion of telehealth and medication delivery (29–31). Provincial and municipal governments have also introduced programs to increase access to supportive housing, through the purchase of hotels and re-appropriation of other public facilities with increased access to harm reduction interventions (32–34), and announced expansions of inpatient detoxification services in some settings to manage the increased demand for these services (35, 36).

Implementation of Risk Mitigation Guidance

On March 26, 2020, the BC Government announced new interim Risk Mitigation Guidance (RMG) to: 1) prevent the spread of COVID-19 by enabling physical distancing and self-isolation among people who use substances and 2) as harm reduction response to the increasingly toxic drug supply as a result of the pandemic (37). The RMG permits prescribing of opioids, stimulants, benzodiazepines, as well as medication alternatives to alcohol and nicotine use, for persons who are COVID-19-positive or at high-risk of infection, combined with a high likelihood of withdrawal, overdose, or other drug-related and systemic harms. In principle, the availability of medication alternatives to illicit substances would also reduce the risk of exposure to and transmission of COVID-19, by reducing drug seeking.

Prior randomized controlled trials (RCTs) provide indirect support for the impetus supporting RMG implementation. Among people with opioid use disorders who were unable to be retained in treatment with oral opioids like methadone or buprenorphine, a number of RCTs have demonstrated that injectable diacetylmorphine and hydromorphone are safe, effective, and cost-effective treatments (38–40). In the absence of wide-spread expansion of injectable OAT, hydromorphone tablet distribution programs have been implemented in recent years to provide alternatives to the toxic drug supply and reduce the risk of fatal overdose (41, 42).

Although more evidence is needed, there is emerging support for the RMG as it pertains to substances other than opioids. A recent meta-analysis of RCTs has concluded that dextroamphetamine can have a clinically significant benefit in promoting abstinence among people with cocaine use disorder (43). Among people with amphetamine use disorder, promising results have been demonstrated in reducing craving and use, and improving retention, where robust doses of psychostimulants have been prescribed (44–46). Among people with alcohol use disorder, a number of RCTs have demonstrated that anticonvulsants such as carbamazepine (47–52) and gabapentin (53, 54) and clonidine (alpha-2 adrenergic agonist) (55, 56) are as safe and effective as benzodiazepines for the management of alcohol withdrawal symptoms. Long-acting benzodiazepines such clonazepam have been used to safely and effectively taper patients off of shorter-acting benzodiazepines such as alprazolam (Xanax ®) (57). Randomized controlled trials are ongoing to test the effectiveness of different pharmacological approaches to managing benzodiazepine use disorder and discontinuation, bearing in mind side-effects, benefits, and risks (58).

Aforementioned studies have been conducted as evaluations of pharmacological treatment options, with the explicit goal of cessation of illicit drug use or abstinence. Furthermore, they have been generated from highly controlled studies, where medications have been consumed under the supervision of health care providers to promote adherence and monitor adverse events. It is likely that the positioning of the RMG as a means of reducing drug-related harm, rather than an explicit form of pharmacological treatment, and its delivery in real-world settings may draw clients who are not directly comparable to persons recruited in the aforementioned trials conducted in controlled conditions with strict eligibility criteria (for instance, screening out individuals with moderate or severe mental health conditions, which are common in people with substance use disorders) (59). Furthermore, the reach of the intervention across the province, and the fidelity to the initial recommendations stated in the RMG is unknown. The RMG only lists oral opioids (i.e. tablet hydromorphone, M-eslon) which have not been the subject of the same rigorous evaluations of safety or effectiveness for the treatment of opioid use disorder in comparison to injectable treatments. In summary, while prior RCTs (39) have informed the opioid options listed in the RMG, the results of these trials are not immediately comparable to the medications listed in the RMG.

The Guidance outlines eligibility based on individual risk of COVID-19 infection, those confirmed COVID-19 positive, or those with a suspected case (e.g., symptomatic and self-isolating); those with a history of ongoing active substance use (opioids, stimulants, alcohol, benzodiazepines, or tobacco); those that are deemed at high risk of withdrawal, overdose, craving, or other harms related to drug and alcohol use. Youth aged < 19 may be eligible if there is informed consent by the client or parent to receive this intervention and additional education is provided. It is noted that prescribers should first offer alternative options (e.g., OAT). Clinical assessment includes current and past substance use, history of overdose, comorbid mental and physical conditions, prescribed medication(s), and access to a prescriber. For persons who do not have a primary care provider (general practitioner/family doctor, or nurse practitioner), or in cases where the primary care provider declines the service, rapid access addiction services and OAT clinics have accepted new patients seeking medications through the RMG. Table 1 provides a full list of the medications identified in the RMG. The medications are accessed free-of-charge to BC residents under the province's PharmaCare program (37).

Table 1 Drug Identification Numbers of medications included in the Risk Mitigation Guidance

Drug type/drug sub-type	Drug Identification Numbers DIN/PINs
Opioids	
Hydromorphone	2364158, 786543, 2225255, 2192144, 2245705, 2337274, 885428, 2319446
M-Eslon	2019930, 2019949, 2019957, 2019965, 2177749, 2177757
Stimulants	
Dextroamphetamine	2448319, 2448327, 2481464, 2481472, 181439, 181447, 1924559, 1924567, 27065, 1924516, 2443236
Methylphenidate	2441934,2441942,2441950, 2441969,2249324, 2249332, 2273950,2330377, 2452731, 2452758, 2452766, 2266687,2326221, 2326248, 2326256, 2243222, 422975, 422983, 2126486, 2126494, 2246991, 584991, 585009, 2234749, 2413728, 2413736, 2413744, 2413752, 2230321, 2230322, 2247364, 5606, 5614, 5185, 632775, 2320312, 2315068, 2315076, 2315084, 2315092
Benzodiazepines	
Clonazepam	2365243, 2365251, 2365278, 2177889, 2177897, 2230366, 2230368, 2230369, 2344602, 2344610, 2442027, 2442035, 2442043, 2442051, 2340968, 2235370, 2237277, 2340976, 2235379, 2237278, 2220598, 2220601, 2344629, 2270641, 2270668, 2270676, 2130998, 2131013, 2131005, 2224100, 2230950, 2230951, 2173344, 2173352, 2236947, 2145227, 2145235, 2145243, 2236948, 2179660, 2048701, 2048728, 2048736, 2207818, 2311593, 2311607, 2311615, 2103656, 2103737, 2242077, 2242078, 382825, 382841, 2233960, 2233982, 2233985, 2239024, 2239025, 2303310, 2303329, 2303337, 2345676,2303302
Diazepam	2247173,2247174, 2247176, 2238162, 362158, 405329, 405337, 434388, 434396, 313580, 2243240, 2386143, 399728, 2385392, 466891, 466905, 303461, 396230, 2137399, 272639, 272647, 280429, 276650, 276642, 272450, 272434, 272442,2247490, 2247491, 2247492, 891797, 13293, 13277, 13285, 12874, 13110, 13757, 13765, 13773, 2065614, 2005492, 602825, 22123106
Alcohol	
Carbamazepine	402699, 2242908, 2242909, 2247135, 578460, 2413590, 2413604, 2243511, 2243512, 2231670, 2238222, 2238223, 504742, 2241882, 2241883, 2042568, 2238640, 2238641, 667110, 2231540, 2231541, 2231542, 2231543, 2231544, 2406861, 2261855, 2261863, 2261839, 2261847, 2367394, 2407515, 2244403, 2244404, 2237907, 2237908, 2052423,2194333, 10405, 369810, 665088, 773611, 755583, 782718
Gabapentin	2256142, 2256150, 2256169, 2477912, 2477920, 2477939, 2293358, 2293366, 2244304, 2244305, 2244306, 2341891, 2341905, 2341913, 2341875, 2341883, 2321203, 2321211, 2321238, 2428334, 2428342, 2365022, 2365030, 2365049, 2365006, 2365014, 2266768, 2450143, 2450151, 2450178, 2450186, 2450194, 2243743,2243745, 2258153, 2258161, 2238671, 2238672, 2238673, 2246314, 2246315, 2246316, 2273853, 2304775, 2304783, 2304791, 2342650, 2342669, 2342677, 2353245, 2353253, 2353261, 2388200, 2388219, 2403757, 2403765, 2403773, 2403781, 2403803, 2431289, 2431297, 2249367, 2249375, 2249383, 2304805, 2304813, 2332582, 2332590, 2332604, 2416840, 2416859, 2416867, 2392526, 2392534, 2285819, 2285827, 2285835, 2285843, 2285851, 2410990, 2411008, 2390949, 2390957, 2390965, 2361469, 2361485, 2361493, 2402289, 2402297, 2391473, 2391481, 2391503, 2432072, 2432080, 2408880, 2408899, 2408902, 2248259, 2248260, 2248261, 2397471, 2397498, 2239717, 2239718, 2084260, 2084279, 2084287, 2384973, 2384981, 2246742, 2246743, 2246744, 2427397, 2258005, 2258013,2243446, 2243447, 2243448, 2255898, 2255901, 2450097, 2450100, 2450119, 2450127, 2450135, 2310449, 2310457, 2310465, 2310473, 2310481, 2319055, 2319063, 2319071, 2260883, 2260891, 2260905, 2260913, 2260921, 2251167, 2251175, 2251183, 2259796, 2259818, 2250888, 2250918, 2250926, 2244513, 2244514, 2244515, 2247346, 2248457, 2431408, 2431416, 2431424, 2432544, 2432552
Clonidine	2248732, 868949, 868957, 2360861, 2360888, 2360896, 259527, 291889, 2361299, 2361302, 2361310, 1910396, 1908162, 519251, 2247607, 2247608, 2462192, 2462206, 2358565, 2358581, 2358603, 1913786, 1913220, 2046121, 2046148, 2304163, 22123091,22123089, 22123090, 22123232,291870
Footnote: ER: extended release; IR: Instant release; DIN: Drug Identification Number; PIN: Product Identification Number; RMG: Risk mitigation guidance	
DIN/PINs reflect medications included in the first iteration of the Risk Mitigation Guidance dated March 26th 2020.	

Study Objectives

There is a critical need for comprehensive assessment of the implementation and impacts of the RMG on COVID-19 transmission and risk of overdose in BC. We anticipate uptake to be uneven across the province given variation across prescribers in education and resources, as well as variation in local and regional resources, services and supports. Prescribers and allied health care professionals are tasked with developing models of service delivery for RMG while simultaneously adapting to new clinical guidance and strains on their practice in addressing the COVID-19 pandemic. In BC as elsewhere, the system of services and supports for people who use substances is complex and services are provided in a variety of settings, including community health centers, specialized residential and outpatient treatment, OAT clinics, and a mixture of peer-run and professionally-led overdose prevention/supervised consumption sites, among others.

This protocol outlines the approach for a mixed methods study of the implementation of RMG and its impacts on COVID-19 infection and drug-related harms, including overdose. Specific objectives are to:

1) Determine the impact of RMG on COVID-19 infection, non-fatal/fatal overdose, all-cause mortality and continuity of care for substance use disorder and other concurrent health conditions.

2) Determine the impact of RMG on the uptake of public health measures to reduce the spread of COVID-19, as well as other behavioural and psychosocial outcomes among people who use substances.

3) Identify individual, interpersonal, and systemic barriers and facilitators to RMG implementation based on program uptake from the perspectives of people who use substances, prescribers and other health service providers.

This study evaluates the RMG as a policy intervention introduced into BC's health system in March 2020, in the context of dual public health emergencies. In terms of the clinical intervention supported by this policy, our focus is on the receipt of a RMG prescription of pharmaceutical alternatives for opioids, alcohol, stimulants, benzodiazepines and other drugs. It should be noted that referral to managed alcohol programs is also mentioned in the RMG as an alternative for providers to consider in supporting people who have alcohol use disorders. However, for pragmatic and methodological reasons, we opted to restrict our study on RMG prescription-based interventions, to the exclusion of related programs or services that offer other forms of support. A parallel evaluation by the Canadian Managed Alcohol Study team (www.cmaps.ca) is ongoing to evaluate the emergence of managed alcohol programs as part of the response to COVID-19.

Methods

Study Design

We will achieve the above objectives through a parallel mixed methods study, with convergent collection and analysis of quantitative and qualitative data (60, 61). The full study involves both primary data collection, including a longitudinal (10-week) observational study, cross-sectional survey, and qualitative interviews, as well as analysis of administrative health data. These components are described in turn. A timeline for the study is provided in Fig. 1.

The study uses an integrated knowledge translation approach, with stakeholders variously involved in all phases of the research. Study governance is provided by a core team of scientific leads, who report to members of two organizations of people with lived/living experience (PWLLE) of substance use, service providers, health planners, policy-makers, and research experts. Separate working groups have been convened to support the analysis of administrative health data and primary data collection components of the study. The primary data collection component is explicitly participatory, with deep involvement of PWLLE including Indigenous PWLLE as well as Indigenous and First Nations community members involved in designing data collection tools, recruitment processes, analysis and knowledge translation. Core team members include representatives from the provincial health authority that oversees health care to First Nations communities (i.e., The First Nations Health Authority, FNHA), a peer network embedded within the BC Centre for Disease Control (Professionals for Ethical Engagement of Peers, PEEP), and a network of independent, autonomous grass-roots drug user groups from across the province (BC/Yukon Association of Drug War Survivors, BCYADWS).

Theoretical Framework

The study is grounded in the Consolidated Framework for Implementation Research (CFIR)(62, 63), extended to include a concurrent evaluation of outcomes (64). The CFIR has been used to guide implementation research across a broad range of intervention types and settings, including substance use and public health. It consists of 39 theoretical concepts or constructs grouped into five domains capturing determinants affecting implementation of an intervention at the organizational level. The five domains include 1) characteristics of individuals receiving and delivering the intervention (e.g., sociodemographic characteristics, knowledge, skills), 2) characteristics of the intervention (e.g., ease of access, eligibility, models of delivery, 3) process of implementation (e.g., leadership, training), 4) inner setting (e.g., policies, organizational culture, space, staffing), and 5) outer setting (e.g., funding, policies, laws). Attention is given throughout the analyses to align each of these implementation constructs with primary and secondary outcomes (described below). While not all aspects are addressed in every component of the study, qualitative and quantitative primary and secondary data will be interpreted with consideration of this framework.

For transparency, we have used two reporting standards checklists: the TIDIeR checklist for the intervention and SPIRIT checklist for the study protocol (65, 66).

Study Population

The study population includes people who use substances and health service providers who work with people who use substances in BC. Eligibility criteria vary somewhat across study components (described below), but are designed to collectively capture the primary stakeholders of the RMG intervention.

Longitudinal and cross-sectional observational study: Recruitment and data collection

People who use substances will be recruited to complete surveys as part of an observational study, with longitudinal and cross-sectional arms (Fig. 2). Posters and online advertisements will be shared by community organizations and social influencers at venues frequented by people who use drugs. Each poster provides contact information (e.g., toll-free number, email address). Upon contacting the study team, participants will be screened for eligibility. Eligibility criteria include being 19 years old and older and having used illicit substances in the past 6 months. Those who received their first RMG prescription within the past 2 weeks, are currently attempting or intending to access a RMG prescription in the next 2 weeks (at time of recruitment) will be eligible for the longitudinal study (target n = 200). They will be asked to complete the survey five times at 2-week intervals (follow-up period = 10 weeks). Given variation in access to providers and programs that support RMG, it is expected that the longitudinal sample will include a mix of respondents who were and were not successful in accessing RMG during the 10-week follow-up period. Those who received their first RMG prescription longer than 2 weeks ago (at time of recruitment) will be eligible for the cross-sectional arm of the study and will complete the survey once only (target n = 200).

Recruitment strategies will be monitored carefully and adapted as needed to ensure that the final samples will permit analytical comparisons by access to RMG. For both the cross-sectional and longitudinal survey arms, attention will be paid during recruitment to ensuring representation by sex/gender, rural/urban setting, substance type (opioids, stimulants, benzodiazepines, and alcohol), and Indigenous ancestry. All eligibility and sampling criteria are determined by self-report.

The surveys (baseline and follow-up) will assess access to RMG prescriptions, ability to implement public health guidelines for COVID-19 (e.g., physical distancing, self-isolation, mask-wearing, access to testing and treatment), substance use and related harms, sources of income (including acquisition crime and sex work), health-related quality of life (EQ-5D-5L) (67, 68), and mental health (PHQ-2 and GAD-2) (69, 70). These domains have been selected in

accordance with the RMG and through consultation with PWLLE on anticipated impacts. With the exception of bespoke items on COVID-19, measures have demonstrated reliability and validity in use with people who use substances.

Qualitative interviews: Recruitment and data collection

A subsample of survey participants (people who use substances) will be recruited for qualitative interviews (n = 40). Interview participants will be purposively sampled to obtain representation by sex/gender, health region, and substance type as well as whether the participant was successful in accessing a RMG prescription. Lead by FNHA, an additional 20 interviews will be conducted with people who identify as Indigenous (First Nations, Inuit or Métis) for a total of 60 interviews with PWLLE.

Interview guides have been developed to align with the Consolidated Framework for Implementation Research (CFIR), assessing facilitators and barriers to implementation across the five domains of the CFIR (62). Focus will be placed on capturing experiences of access to RMG and aspects of delivery models. Facilitators and barriers will be explored across and within CFIR domains to create a comprehensive understanding of implementation and implications for programming. FNHA investigators and Indigenous stakeholders (e.g., PWLLE, First Nations community members) have designed a separate interview guide for the subsample of Indigenous participants to yield culturally relevant findings on RMG implementation and to inform FNHA policy and programming and support for First Nation communities, particularly rural and remote communities. In BC, Indigenous people who use substances have been disproportionately impacted by the overdose emergency (71, 72) and experience elevated and intersecting barriers accessing health care services (e.g., stigma and discrimination, geography).

Additional interviews will be conducted with service providers and heath planners (n = 40) who are involved in RMG delivery and those who opt not to participate in RMG delivery. We will purposively recruit providers from different disciplinary backgrounds: prescribers (physicians and nurse practitioners), pharmacists, nurses, and harm reduction workers. Interview guides will be constructed as above using CFIR interview templates, structured to assess facilitators and barriers to implementation across the five domains. This will yield information on provider knowledge of and level of comfort with the RMG, as well as information needs, and personal and organizational goals, philosophies and models for service delivery.

Analysis of administrative health data: Data source and linkage

Population-based analyses will be conducted using linked administrative health datasets that capture health care utilization across the province. In BC, medically necessary health care is covered by universal health insurance, through a single-payer, government administered plan that is available to all registered residents of the province. The plan covers most hospitalizations, acute and emergency care, primary care, and some mental health and substance use services. Prescription pharmaceuticals are covered for selected medical diagnoses and populations; however, records for all dispensations are retained regardless of the public or private health insurance payer. Health benefits for First Nations in BC are administered by the First Nations Health Authority (FNHA). Datasets capturing these different sectors of health care will be accessed and linked for analysis (Table 2).

Table 2 List of linked administrative health data sources

Database	Description	Generating process
BC COVID-19 Cohort (BCC19C)	The BCC19C is being established at the Provincial Health Service Authority as a surveillance platform to integrate various datasets including data on BC-wide laboratory tests, COVID-19 surveillance case data, HealthLink 811 calls, prescription drug dispensations, medical visits, ambulance dispatches, Intensive Care Unit (ICU) admissions, and mortality - all integrated with existing administrative data sources such as the Chronic Disease Registry, hospital admissions and the provincial client roster.	Data are provided by BCCDC, PHSA and MoH. These datasets are linked through Public Health Reporting Data Warehouse (PHRDW) linkage algorithm, which is a probabilistic algorithm utilizing PHNs, names and date of birth to improve accuracy. All records which are linked to a single person through matching, a patient master key is assigned and identifiers are removed. Data with patient master key without identifiers is then loaded to the analytic environment, which is hosted in a secure Microsoft cloud. This project and environment is going through Privacy Impact Assessment as standard procedure for hosting health data for surveillance purposes. Linkage algorithm and de-identification process used in this project is standard process which has been used in PHRDW for many years.
Vital Statistics	All deaths registered in the province.	Data is checked against nationally uniform vital registration and statistics standards.
BC Coroner's Service database	The coroner investigates all unnatural and unexpected deaths (including illicit drug overdose deaths), all children's deaths, all medically assisted deaths, all deaths in custody, and all deaths in designated institutions in BC. Data contains information about date of death/injury, age group, occupation and gender of decedent, location of death, location of residence of the decedent, cause(s) of death, frequency of drug use and route of administration, toxicology results, and history of recent incarceration.	The agency maintains a database and conducts ongoing surveillance of common causes and circumstances of death.
PharmaNet database	All prescriptions for drugs and medical supplies dispensed from pharmacies including hospital outpatient dispensations.	Electronically submitted by pharmacists dispensing medications in real time. Required for reimbursement.
Discharge abstract database (DAD)	All hospital discharges, day surgery, transfers, and deaths of inpatients. Data of BC residents treated at hospital out of province, and out-of-province residents treated within BC hospitals included.	Data files grouped into fiscal years by separation date (not admission date). Each hospital submits electronic records of patient visits to the provincial government which cleans and then submits the records to the Canadian Institute for Health Information (CIHI). CIHI regularly conducts re-abstraction to ensure data quality.
Medical Services Plan (MSP) database	All medically necessary services provided by fee-for-service practitioners covered by the province's universal insurance program: Medical Services Plan (MSP).	Majority of billing records submitted electronically by practitioners' offices for reimbursement purposes. Diagnosis codes accurate only to 3rd digit.
BC corrections database	The Provincial Health Officer compels Corrections Data from the Ministry of Public Safety and Solicitor General. BC corrections data includes date of intake into and discharge from the correctional system, discharge location, and reason for release.	The Ministry of health receives inmate client file, inmate event file and inmate event movement files from the Public Safety and Solicitor General. The Ministry of Health Data Provisioning Team anonymizes client ID and personal health numbers and provides an anonymized version of the Client File that contains anonymized IDs.
National Ambulatory Care Reporting System (NACRS) Database	All hospital-based and community-based ambulatory care including day surgery, outpatient and community-based clinics emergency departments	Data is collected directly from participating facilities or from regional health authorities or ministries of health.
BC Perinatal Data registry	Perinatal Services BC houses the provincial perinatal database, which consists of data collected from obstetrical facilities as well as births occurring at home attended by BC Registered Midwives.	Perinatal data is collected from facilities throughout the province and imported into the central BC Perinatal Data registry. Installation hospitals have the same software as the central system, and send data on a periodic basis to the provincial database. The non-installation hospitals have their databases maintained at the central office. Data from the Canadian Institute for Health Information (CIHI) and matched files from the British Columbia Vital Statistics Agency complement the data elements. Participation in the registry is not mandatory.
Social development and Poverty Reduction	Persons who received income or disability assistance by the Ministry of Social Development and Poverty Reduction. The data contains type of assistance program, family type, a number of dependents, payment, and homelessness flag.	Data is extracted from the Ministry of Social Development and Poverty Reduction's records of social assistance or disability assistance payments that have been made to individuals under the BC Employment and Assistance program.
First Nation client file*	A cohort of BC Resident First Nations people registered under the Indian Act, and their unregistered descendants for whom entitlement-to-register can be determined, linkable on their BC Ministry of Health Personal Health Number.	Data collected from Aboriginal Affairs and Northern Development is being matched annually against BC's databases to create the First Nations Client File.

DAD: Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; MSP: Medical Services Plan *Restricted use – at the discretion of the First Nations Health Authority

The Provincial substance use disorders (SUD) cohort is an administrative database that captures all BC residents with an indication of SUD since 1996 (73, 74). The cohort is identified using eleven linked population-level administrative databases, capturing provincial health insurance plan registration, physician billing records, hospitalizations, medication dispensations, health services delivered within provincial prisons, emergency department visits, perinatal services for all provincial births, receipt of housing and income assistance, mortality and cause of death including toxicology analysis.

In addition to the provincial SUD cohort, records from the COVID-19 Cohort will be accessed for this study. The COVID-19 Cohort, held at the BC Centre for Disease Control, includes medication dispensations, mortality and COVID-19 polymerase chain reaction testing records. For both cohorts, linkage across datasets is accomplished at the record-level via unique Personal Health Numbers. Both cohorts will be refreshed to capture data through the end of 2020.

Outcomes and implementation processes

Primary and secondary outcomes and implementation process indicators are defined in Table 3, along with their data source (whether captured in the longitudinal/cross-sectional survey, qualitative interviews, or administrative health data). Primary outcomes are COVID-19 infection and fatal/non-fatal overdose. These outcomes were identified explicitly in the RMG and/or are expected (based on supporting literature and/or discussion with stakeholders) to be most directly impacted by the RMG. Secondary outcomes capture effects that are expected to be intermediates on the causal pathway between RMG exposure and primary outcomes (e.g., continuity of care), or that may be expected to shift given RMG exposure but that are influenced by a greater array of factors external to the RMG (e.g., health-related quality of life, mental health, illicit substance use). Secondary outcomes were typically identified as important factors to consider by stakeholders (including people with lived and living experience of substance use). They are included here to support broader exploration of the effects of programs that offer people who use substances a “safer supply”. Finally, a suite of implementation process indicators has been defined to align with the domains of the CFIR.

Table 3 Primary and secondary outcomes, and implementation process indicators

Outcome	Rationale, Description	Data source(s)
Primary Outcomes		
Incidence of SARS-CoV-2 infection	According to the initial impetus for the Risk Mitigation Guidance.	Public Health Laboratory system
Incidence of fatal overdose*	Coroner's record with laboratory testing confirming presence of a range of substances. Concordance of these classifications will be confirmed with linked vital statistics data.	BC Coroner's service database; BC vital statistics database.
Incidence of non-fatal overdose*	ED visit or hospitalization for drug-related causes.	NACRS, DAD databases.
Secondary Outcomes		
Incidence of all-cause mortality	We will consider all-cause mortality to account for the uncertainty in attribution of illicit drugs in mortality records, and otherwise acknowledge the secondary role of drug use in deaths due to other causes.	BC Coroner's service database; BC vital statistics database.
Incidence of all-cause acute care visits to hospital, emergency department***	We will consider all-cause acute care visits to account for the uncertainty in attribution of illicit drugs in health administrative records, and otherwise acknowledge the secondary role of drug use in causes of other hospitalizations.	NACRS, DAD databases.
OAT retention among people with OUD	We will consider variations of definitions, including (but not limited to) OAT episode discontinuations^, missed doses^^ and sustained disengagement^^^.	PharmaNet, DAD database
Retention/continuity of care for other chronic medical conditions	The medical conditions under consideration will include HCV, Mental health disorders and potentially other conditions cited in consultations with community stakeholders.	PharmaNet, MSP, DAD
Uptake of COVID-19 protective measures	Differences in ability to maintain physical distancing and self-isolate when needed, based on RMG exposure	Longitudinal survey data
Health-related quality of life	Differential change (over 10 weeks) in scores on the EQ-5D-5L, based on RMG exposure	Longitudinal survey data
Mental health	Differential change (over 10 weeks) in scores on the PHQ-2/GAD-2, based on RMG exposure	Longitudinal survey data
Substance use and related harms	Differential change (over 10 weeks) in use of illicit opioids, stimulants, and benzodiazepines (without a prescription), and in binge drinking, based on RMG exposure	Longitudinal survey data
Income source	Differential change (over 10 weeks) in sex work and acquisition crime as income source, based on RMG exposure	Longitudinal survey data
Implementation Outcomes		
Number of people who receive an RMG prescription**	Measure of access to RMG (CFIR domain: characteristics of the intervention)	PharmaNet
Number of prescribers writing RMG prescriptions	Measure of access to RMG (CFIR domain: characteristics of the intervention)	PharmaNet
Extent to which access varies by geography and population subgroup	Measures of variability in access to RMG (CFIR domain: characteristics of individuals receiving and delivering the intervention)	PharmaNet
Extent to which delivery differs across the province	Service provider descriptions of who is eligible for RMG and models of delivery (CFIR domain: process of implementation)	Qualitative interviews, longitudinal and cross-sectional survey data
Extent and types of barriers encountered in accessing RMG	Descriptions by people who use substances of barriers encountered in accessing RMG (CFIR domains: intervention characteristics, inner and outer context)	Qualitative interviews, longitudinal and cross-sectional survey data
Extent to which providers feel ready and able to implement RMG	Descriptions of perceived knowledge, skills, training, organizational and system supports (CFIR domains: all)	Qualitative interviews, longitudinal and cross-sectional survey data

DAD: Discharge Abstract Database; ED: Emergency Department; EQ-5D: Euro-Qol 5 dimension; NACRS: National Ambulatory Care Reporting System; MSP: Medical Services Plan; PWOUD: people with opioid use disorder. *drug-related causes classified through ICD-9/10 codes presented in Table A1. ** according to both definitions 1 and 2; *** Our ED data did not have complete coverage for all visits in BC. The estimated ED coverage in NACRS was 72% from 29 ED facilities submitting to NACRS. ^: ≥ 5 consecutive days of missed methadone doses or ≥ 6 consecutive days of missed buprenorphine/naloxone doses; ^^: any missed doses within an continuous episode; ^^^: OAT disengaged ≥ 3, 6, or 12 months.

RMG exposure

Receipt of RMG prescriptions will be elicited via self-report in primary data collection, and identified through administrative health data on medication dispensations. Relevant to the definition of RMG exposure in the administrative health data, medications dispensed through RMG were already being used for therapeutic purposes, and thus had Drug Identification Numbers (DINs) assigned to them. When RMG was implemented new DINs were not assigned. Physicians were instructed to add free-form codes to the directions for use field on the RMG prescriptions to differentiate them from other routine care. We developed algorithms to identify RMG recipients by applying restrictions to our case searches using prescription data from PharmaNet including: prescription history (prior RMG medication prescription records), timing (start date, duration), dispensation frequency (i.e. daily) and drug type (by DIN) (Table 4). From cases identified by these initial restrictions, a list of keywords was developed from the free-form codes written in the directions for use variable. A fuzzy string search of the keywords was applied (75). The fuzzy logic allowed for incomplete, truncated or commonly misspelled words to be captured in the keyword search. The keyword list was then further refined based on consultation with prescribers (who participate in the study consortium).

Table A1 ICD-9/10 and drug identification numbers used to draw the provincial SUD cohort

Database	Code no.*	Description
PharmaNet	999792, 999793, 66999990, 66999991, 66999992, 66999993, 66999997, 66999998, 66999999, 67000000, 67000001, 67000002, 67000003, 67000004, 67000005, 67000006, 67000007, 67000008, 67000009,67000010, 67000011, 67000012, 67000013, 67000014, 67000015, 67000016, 67000017, 67000018, 67000019, 67000020	DIN/PIN for methadone as OAT
PharmaNet	2295695, 2295709, 2408090, 2408104, 2424851, 2424878, 2453908, 2453916, 2468085, 2468093	DIN/PIN for buprenorphine/naloxone as OAT
PharmaNet	2242963, 2242964, 2474921, 2483084, 2483092, 66999995, 66999996	DIN/PIN for buprenorphine
PharmaNet	22123349, 22123346, 22123347, 22123348	DIN/PIN for slow release morphine
PharmaNet	2146126, 22123340, 22123357, 66123367,	DIN/PIN for injectable OAT[†]
PharmaNet	786543, 885428	DIN/PIN for t-IOAT hydromorphone
PharmaNet	2293269, 2158655, 2213826, 2444275, 2451883, 2534, 2542, 2041375, 2041391, 66124089, 66124085, 66124087, 66129170	DIN/PIN for naltrexone, acamprosate, disulfiram as medication of alcohol use disorder
MSP	39, 15039, 13013, 13014, 36521	Fee items related to OAT
MSP/DAD/BCPDR	291, 292, 303, 304, 305, 357.5, 425.5, 535.3, 571, 648.3, 655.4, 655.5, 760.7, 779.5, 965.0, 967, 969, 970, E850, E851, E852, E853.2, E854, V65.42	ICD9 for drug abuse and poisoning
MSP/DAD/BCPDR/VS	F10-F16, F19, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, P04.4, P96.1, Q86.0, T40, T42.4, T43.6, X42, X62, Y12, Z50.2, Z50.3, Z71.4, Z71.5, Z72.1, Z72.2	ICD10 for drug abuse and poisoning
NACRS	F100, F103, F119, F139, F149, F159, F169, F199, K709, T401, T405, T406, T409, T424, T439	ICD10 (diagnosis shortlists) for drug abuse and poisoning
BCPDR	“Substance use during pregnancy – Any”): Heroin/opioids, cocaine, methadone, solvents, or marijuana; OR care provider lists use of prescription, 'other', or unknown other drug as a risk to the pregnancy and their babies.	Free Text variable

Abbreviations: DAD: Discharge Abstract Database; MSP: Medical services Plan; BCPDR: BC Perinatal Data Registry; *PharmaNet database: Drug Identification Numbers (4)/Product Identification Numbers(PIN) used for identification; MSP, DAD, Vital statistics databases: ICD-9/10 codes used for cohort identification; [†]Diacetylmorphine or hydromorphone dispensed in certain pharmacies.

Table 4 Algorithms to identify RMG exposure

Step 1 Case Definition 1: Higher specificity lower sensitivity For each chemical type, person NOT on RMG medication in the 2 months prior to March 27, 2020, but prescribed medication after March 27, 2020 with one of the following keywords in the directions for use variable: *corona, coronavir, coronavirus, coronavirus, covid, covid19, crisis, mitigat, mitigati, mitigatio, mitigation, pande, pandem, pandemic, pandemic withdrawal management, pprm, pwm, risk mit, risk mitigation, riskmitigation, safe supp, safe suppl, safe supply, safer supply* *Exclusion: "pain" in directions for use variable Case Definition 2: Higher sensitivity, lower specificity For each chemical type, person NOT on RMG medication in the 2 months prior to March 27, 2020, but prescribed medication after March 27, 2020 with one of the keywords in the directions for use variable as listed in definition 1 or any of the following keywords in the directions for use variable: *carries, carry, craving, deliv, delivery, dispense + deliver, dispense + delivery, dispensecarries, distancing, emerge, emergen, emergenc, emergency, emergency supply, guidan, guidanc, guideline, guidelines, illici, illicit, interim, isolatio, isolation, management, outbreak, overdo, replacement, risk, safer, suply, supply, unwit, unwitne, unwitness, unwitnessed, withd, withdr, withdra, withdraw, withdraw, withdrawa, withdrawal, witness, witnessed* *Exclusion: "pain" in directions for use variable Step 2 AND application of the following criteria for alcohol withdrawal and benzodiazepine cases only: Exclusion criteria: Persons with a record in MSP or PharmaNet for palliative care or cancer on March 27-Dec 31, 2020 and prior to first RMG prescription. Inclusion criteria: Record in MSP for Substance Use Disorder on March 27-Dec 31, 2020 or prior to at least one of their RMG prescriptions.
MSP: Medical Services Plan

As this method may lead to a degree of misclassification, we developed two case definitions: one which we anticipate will have a lower sensitivity and higher specificity and an alternative with higher degree of sensitivity but lower specificity. While the definition with higher sensitivity will serve as our baseline definition of exposure to the RMG program, the alternative will be used to assess the robustness of our results. Analyses will consider potentially differential effects according to medication type, dosage, carry length and persistence, pending sufficient statistical power.

Statistical Analysis

We will conduct analysis of administrative health data in parallel with data collection and analyses of data from surveys and interviews, allowing us to identify early trends in provincial reach and impacts of RMG. Preliminary findings from interim analyses of interview and survey data will be used to guide ongoing analyses of secondary data and the refinement of tools for subsequent primary data collection.

Statistical analysis for Objective 1

The impact of RMG on COVID-19 infection, non-fatal/fatal overdose, all-cause mortality and continuity of care for SUD and other concurrent health conditions will be determined using administrative health data. The analytical approach will capture both the intent to treat and per-protocol effects of RMG dispensations, combine propensity score matching and marginal structural modeling to control for baseline and time-varying potential confounders of the effect of RMG prescriptions on the study outcomes. First, we will apply propensity score matching analysis (76), with both investigator-selected covariates and a high-dimensional propensity scoring methodology using machine learning methods (77), to identify a control group of individuals who were eligible for RMG, and who had similar characteristics as those receiving RMG dispensations, but did not receive RMG prescriptions at any point during study follow-up (March 27, 2020 – December 31, 2020).

Second, the 'per protocol' effect of RMG on outcomes will be estimated using marginal structural models, which are appropriate in situations when time-dependent variables are simultaneously confounders of the effect of interest and are predicted by previous treatment. We hypothesize exposure to RMG at time t affects time-dependent variables including engagement in treatment for substance use disorder, mental health conditions and other medical care at time t + 1, which in turn influences RMG exposure at time t + 2. Time-invariant and time-varying confounding at time t affects RMG exposure, the treatment and confounders at time t + 1. To control for time-varying confounding in the exposure-outcome relationship, inverse probability weights are estimated for each time point of the study to create a pseudo-population in which the exposure is independent of the measured confounders. The pseudo-population is the result of assigning to each participant a weight that is inversely proportional to the participant's probability of receiving her own exposure history. Weighted estimation of the parameters of marginal structural models requires fitting several models: the structural (i.e. weighted) model, the exposure model and the censoring model. Fitted values of separate regression models will thus be estimated for the numerator and denominator of the IPW for each time point. In the numerator, a pooled logistic regression model will be estimated for the probability of RMG receipt, including only the baseline covariates, as well as the number of days on RMG in the previous week. The model used to estimate the denominator of the weight will include the baseline and time-varying covariates, in time t-1. Similar models will be fitted to estimate the probability of censorship.

Selection of both baseline and time-varying covariates will be initially informed by a systematic review of factors associated with fatal and non-fatal overdose. We will also draw from the results of preliminary analyses of survey and interview data, where possible, to identify other potential confounders. The modeling strategy and selected covariates will be reviewed with the consortium prior to the delivery of the final linked dataset.

We propose stratified analyses on four key population groups, including pregnant and parenting (with children ≤ 6 years) women, identified via the perinatal care database; individuals with criminal justice system involvement within 12 months of RMG receipt (using linked data from the Ministry of Public Safety and

the Solicitor General of BC); and a separate, stratified analysis on First Nations people, led by FNHA analysts, in accordance with FNHA data governance and the principles of Ownership, Control, Access and Possession (OCAP®). Additional subgroup analyses may consider RMG recipients with concurrent mental health conditions and those who have received OAT within 12 months of RMG receipt. Subgroup analyses will be considered on the basis of sufficient statistical power. Our a priori assumptions of 3% of those with detected SUD receiving RMG prescriptions and 3% of mortality in this population over the study period indicate 2,121 RMG recipients will be required to achieve 80% power to detect a 30% reduction in the hazard of the primary outcome for RMG recipients compared to control, by using a two-sided log-rank test with 5% significance level. We will adjust the parameters of the power calculation once data is collected, and use this objective criterion to determine the extent of subgroup analysis we can feasibly conduct.

Statistical analysis for Objective 2

The impact of RMG on uptake of public health measures to reduce the spread of COVID-19 and other behavioural and psychosocial outcomes will be determined using data from the longitudinal observational study. We will use generalized estimating equations to assess the effects of RMG on changes over time in ability to maintain physical distancing and to self-isolate as needed, substance use and related harms, income sources, health-related quality of life, and mental health. A modified sandwich variance estimator will be used to correct for downward bias and improve efficiency arising from the small sample size (78). The sample size (n = 200) gives us 80% power to detect a clinically meaningful difference of Cohen's d = 0.4, assuming 30% attrition (final estimated n = 140) (79). In the analysis, attention will be paid throughout to exploring differences by sex/gender, rural/urban setting and substance type (i.e., opioids, stimulants, benzodiazepines, and alcohol). Pending sufficient sample size, distinct analyses using data from participants who self-identified as Indigenous will be designed and executed by FNHA investigators, Indigenous stakeholders and aligned with First Nations community priorities.

Statistical analysis for Objective 3

Facilitators and barriers to RMG implementation will be informed through convergent analyses of quantitative and qualitative data (including data from longitudinal and cross-sectional surveys, qualitative interviews, and administrative health data). This phase of the analysis is informed by the CFIR and centres on the implementation process indicators identified in Table 3. Linked administrative health data will be used to identify the numbers of recipients and prescribers of RMG. Bar graphs and maps will be used to show the uptake of RMG across time and geography. Additional descriptive analyses will look at the characteristics of the population receiving RMG prescription, including sex, substance type, age, region, and neighborhood socio-economic composition.

Qualitative interviews with PWLLE and providers will be transcribed verbatim, read by two researchers and analyzed using NVIVO software. The initial coding framework will be based on the CFIR domains (characteristics of participants), process of implementation, intervention characteristics, inner and outer context), and coding will proceed iteratively with the framework being refined as new themes emerge. Findings will be triangulated with descriptive analyses of quantitative data (collected via longitudinal and cross-sectional data) to examine implementation process indicators on differential understandings of eligibility and models of delivery, barriers that relate to the intervention itself, inner context, and outer context of implementation, and service provider perceptions of readiness, ability, and support **(**Table 3**)**. Additional analyses led by FNHA investigators and Indigenous stakeholders will focus on culturally relevant issues related to RMG implementation, as reported by Indigenous people who use substances.

As a whole, this analytical strategy will provide critical insights into implementation challenges, facilitators, and recommendations for improvements. Consistent with a parallel mixed methods design, this analysis will assist with the interpretation of findings generated in Objectives 1 and 2, particularly variation in patterns of outcomes across measures and key subgroups.

Ethics And Dissemination

Study activities have been developed to adhere to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS-2) (80). All primary data will be collected by phone or online, in accordance with recommended COVID-19 research practices. Ongoing leadership provided by First Nations Health Authority partners and PWLLE who identify as Indigenous on the study team will work to ensure this research continues to be guided by TCPS-2 and the Truth and Reconciliation Commission's Calls to Action related to public health, data governance and research ethics related to Indigenous Peoples (81). Results will be disseminated incrementally, on an ongoing basis, through the consortium established for this study, and then published in peer-reviewed journals.

Discussion

We emphasize that we are undertaking this evaluation in a rapidly-changing context, and thus our evaluation plan may require amendments as the intervention continues to adapt. In the two months prior to the submission of this manuscript, the province granted prescription privileges to registered nurses and registered psychiatric nurses (82), in part a result of the relatively limited reach of the intervention in the 6 months following implementation. Changes to the coding of RMG prescriptions Ongoing engagement with provincial policymakers, clinicians and PWLLE will ensure this study fully captures and characterizes the RMG intervention as it evolves. Furthermore, evaluation of the primary and secondary outcomes and implementation processes will take into account time trends or key dates in assessing the effect of the intervention through different stages of its adaptation. This is a key feature of this evaluation, which we have incorporated following directly from CFIR guidelines (62).

The integrated knowledge translation approach taken in this study is clearly key to its success. Communications on study design and objectives with PWLLE began prior to the development of the funding proposal (in April 2020), with inroads to developing the consortium of stakeholders during proposal development. Formal communications, in the form of consortium meetings, began immediately after funding approval (July 2020). The preparation of this protocol for peer-review constituted an important step in solidifying the aims of the evaluation and providing opportunity for a wide range of stakeholders to engage in and contribute further to the design of the study.

The selected mixed method study design will allow us to model outcomes while also attending to factors related to the implementation across geographies and populations. The design is well suited to evaluating a novel intervention being rolled-out in a unique and changing context. By capitalizing on the strengths of administrative health data (e.g., population reach, longitudinal follow-up), combined with targeted primary data collection on processes and outcomes of RMG, this study will capture the dynamic nature of COVID-19, associated risk mitigation strategies, and secondary effects for people who use substances. By pairing primary data collection with analysis of administrative data, we are able to capture a broad array of health and psychosocial outcomes. Further capture of qualitative data on RMG implementation allow us to better understand what has and has not been realized since the release of the RMG document, and to interpret findings pertaining to outcomes accordingly.

These study design elements are also supported by the unique research context that is available in BC. The province is home to administrative health datasets that are among the most comprehensive in the world, supporting robust population-level health services research. It is also home to multiple provincial networks of PWLLE, both system-embedded and independent drug user groups, which have a long-standing history of engaging in research. Finally, public support for public health approaches to address the harms of substance use has enabled leadership to implement innovative strategies, such as the RMG. Formal and informal polls, reported in local news media, have consistently demonstrated public support for issues such as decriminalization of illicit drugs, anti-stigma campaigns and the use of pharmaceutical alternatives to the toxic drug supply (83–85).

This study constitutes the first formal evaluation of a provincially-sanctioned harm reduction program to provide regulated pharmaceutical alternatives to the toxic drug supply. Variously termed “safe supply”, this initial implementation should be considered a cautious first step towards a broader program to address the contamination of the illicit drug supply. Aside from the assessment of the primary and secondary outcomes, this evaluation will yield critical insights into the success of the initial implementation of RMG, which can in turn be used to further adapt and extend its reach. Additional descriptive analyses on the characteristics of people who do and do not receive a RMG prescription and on service providers will provide further information on fidelity to the initial guidelines and gaps in implementation.

We anticipate that the multiple methods and sub-study designs implemented as part of this project will allow us to address many potential issues that we are likely to encounter. However, we note several limitations. As with any non-experimental policy evaluation, there are threats to the internal and external validity of the study which may not be possible to fully account for or adjust in the proposed analyses. In particular confounding by indication, which may not be fully adjusted in any non-experimental study, is likely in the RMG program. Those accessing RMG may be better connected with the health system, have a stronger attachment to prescribers, and may be potentially more likely to reside in urban centers, where specialty addictions care is more likely. Our proposed analytic approach, using several approaches to adjust for baseline confounding, contrasting against a parallel analysis of longitudinal and cross-sectional observational data, may provide the best possible opportunity to obtain a causal effect of the RMG program on the primary and secondary outcomes. Furthermore, the external validity – both in reference to other jurisdictions and potential future iterations of the program in British Columbia – may be limited. Locally, broader implementation through non-medical settings may draw a different client base whose outcomes may differ from persons included in this initial intervention. Given the vulnerability of the target population and the inherent risk involved in administering even quality-controlled substances, ongoing evaluation and community consultation will be required. All analyses will be interpreted iteratively to ensure that findings from each data source are incorporated into our knowledge translation process.

Abbreviations

BC	British Columbia
BCYADWS	BC/Yukon Association of Drug War Survivors
CFIR	Consolidated Framework for Implementation Research
CIHR	Canadian Institutes of Health Research
DINs	Drug Identification Numbers
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
FNHA	First Nations Health Authority
GAD-2	Generalized Anxiety Disorder 2-item questionnaire
MSFHR	Michael Smith Foundation for Health Research
OAT	Opioid Agonist Treatment
OCAP	Ownership, Control, Access and Possession
OUD	Opioid Use Disorder
PEEP	Professionals for Ethical Engagement of Peers
PHQ-2	Patient Health Questionnaire 2-item
PWLLE	People with lived/living experience
RCT	Randomized Controlled Trials
RMG	Risk Mitigation Guidance
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SUD	Substance use disorder
TCPS-2	Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans
TIDieR	Template for Intervention Description and Replication

Declarations

Ethics approval and consent to participate: Study activities have been developed to adhere to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS-2) (80) and have been approved by the harmonized University of British Columbia Behavioural Research Ethics Board (UBC REB #H20-02052). All primary data will be collected by phone or online, in accordance with recommended COVID-19 research practices. Ongoing leadership provided by First Nations Health Authority partners and PWLLE who identify as Indigenous on the study team will work to ensure this research continues to be guided by TCPS-2 and the Truth and Reconciliation Commission's Calls to Action related to public health, data governance and research ethics related to Indigenous Peoples (81).

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Authors' contributions: BN conceptualized the study, designed the administrative health data analysis plan, and co-wrote the first draft of the manuscript. AS conceptualized the study, designed the administrative health data analysis plan, and co-wrote the first draft of the manuscript. KU conceptualized the study, designed the plan for primary data collection, and co-wrote the first draft of the manuscript. NH conceptualized the study, designed the administrative health data analysis plan, and co-wrote the first draft of the manuscript. HP designed the administrative health data analysis plan and revised the manuscript. KL revised the manuscript. JEM designed the administrative health data analysis plan and revised the manuscript. BZ designed the administrative health data analysis plan. KGC designed the plan for primary data collection and revised of the manuscript. BB revised the manuscript. LM revised the manuscript. CB revised the manuscript. ET revised the manuscript. PBM revised the manuscript. BP conceptualized the study, designed the plan for primary data collection, and co-wrote the first draft of the manuscript.

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Figures

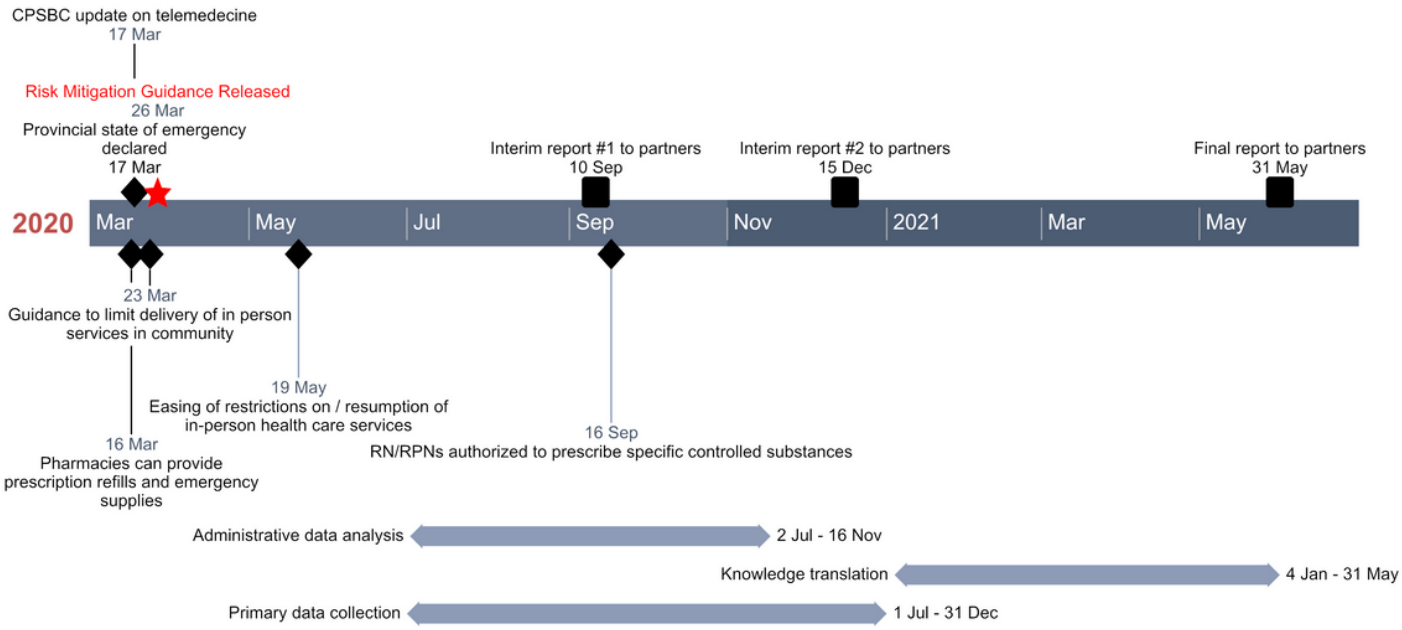


Figure 1

Study Timeline

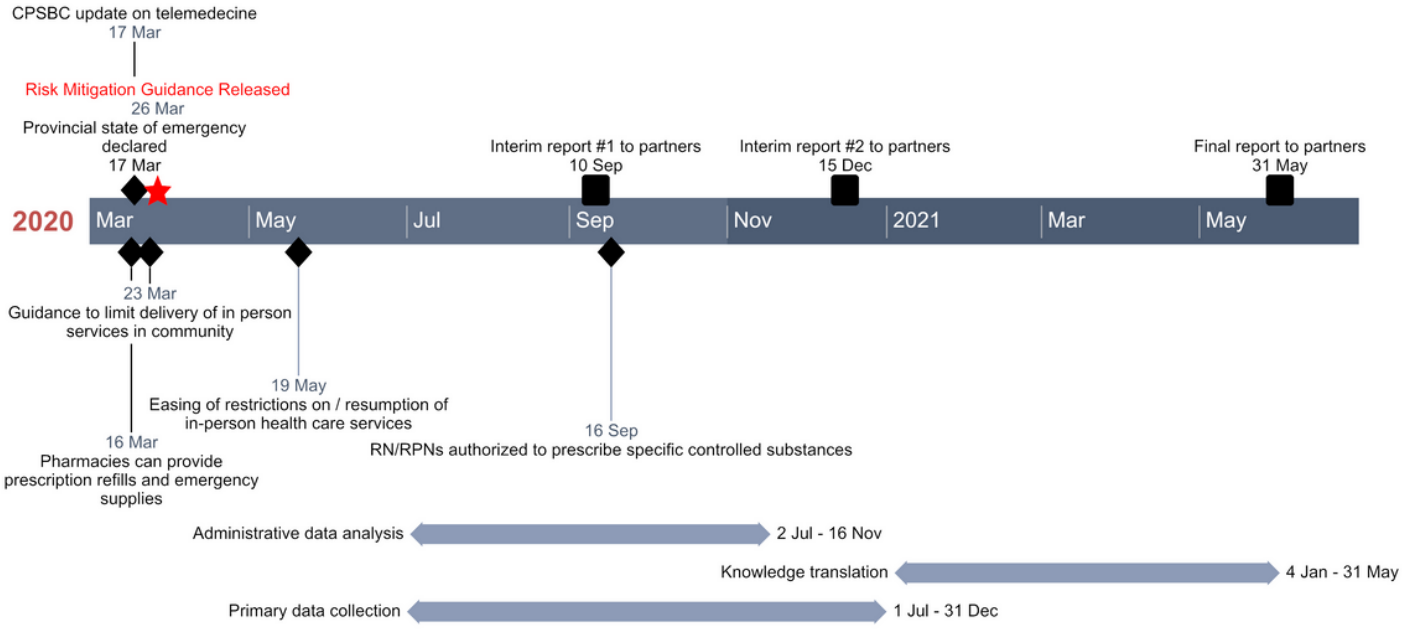


Figure 1

Study Timeline

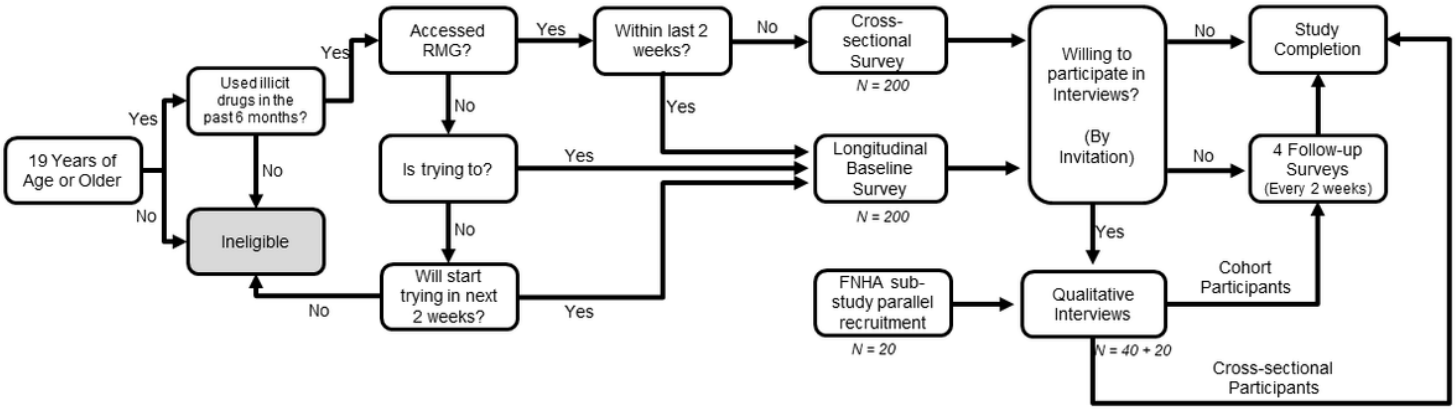
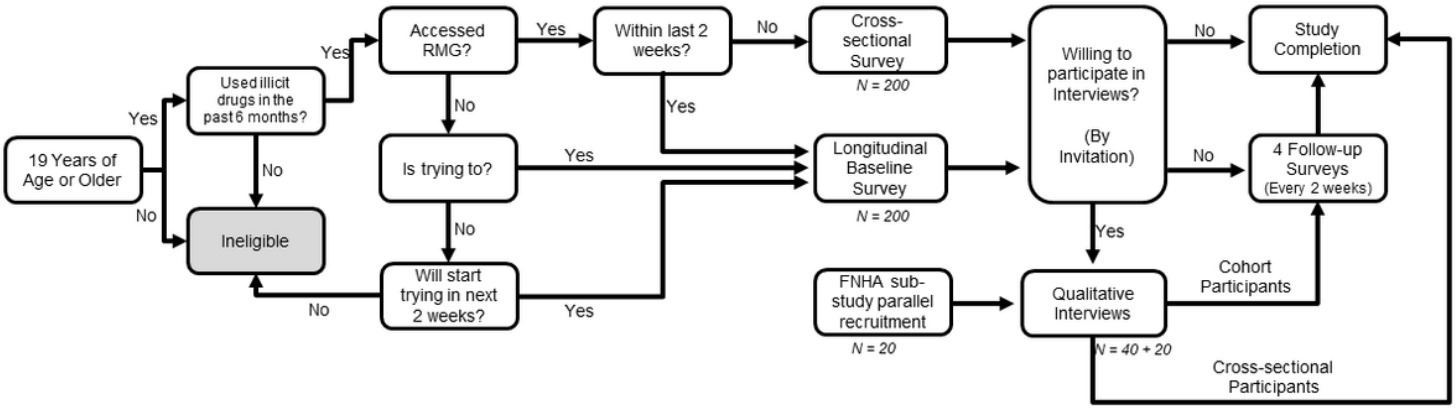


Figure 2

Flow chart for recruitment into the longitudinal and cross-sectional observational study



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