Canadian Research Initiative on Substance Misuse (CRISM): Proposal for an Implementation Science Program on Opioid Interventions and Services

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Contents

CRISM Implementation Science Program on Opioid Interventions and Services

Summary

Canada is experiencing a public health emergency related to medical (prescription) opioids and, in some regions, illicitly produced opioids (e.g., fentanyl, heroin). Services are being expanded in many jurisdictions, but progress is slow and only patchworks of public health interventions and treatment services are currently in place across the country. Without scaling up evidence-based programs in different regions and among different populations, the individual and population burden of opioid use will continue to be high.

This proposal was written in response to CIHR's Request for Applications to the Canadian Research Initiative on Substance Misuse (CRISM) network for a directed grant addressing the opioid emergency (**https://tinyurl.com/y9sgx64x**). CRISM is a unique CIHR-funded national research network of researchers, system managers, people with lived experience, and decision-makers. Its purpose is to conduct research and support knowledge translation to enhance delivery of evidence-based interventions for substance misuse.

CRISM will develop and execute a program in four thematic areas that have high potential for reducing the individual and population burden of opioid use: (1) scaling up public health interventions (i.e., safer consumption services and naloxone delivery); (2) optimizing opioid use disorder treatments (i.e., oral and injectable opioid pharmacotherapy); (3) improving the evidence base for withdrawal management, psychosocial and recovery-based treatment options; and (4) collaboratively developing new intervention approaches to meet the needs of high-risk target populations.

The proposed implementation science program will be developed *purposively*, capitalizing on service innovations that are rapidly being deployed at the regional level; *strategically*, by developing effective longer-term working relationships with groups disproportionately affected by the opioid emergency; and *collaboratively*, through a structured process to engage CRISM member expertise and people with lived experience of opioid problems. The overall aim is to inform and support the implementation of an improved national intervention continuum to address this complex health challenge.

A. Canada's Opioid Emergency

In Canada, as in the U.S., acute and long-term adverse health outcomes related to opioid use have increased substantially over the past decade.[1,2] This growing public health emergency includes increasing rates of non-medical opioid use, opioid-related morbidity, and mortality (e.g., overdose deaths). Although fuelled by increases in non-medical use and diversion of pharmaceutical, medically-dispensed opioids,[3] adverse outcomes associated with the emergence of highly potent illicitly manufactured synthetic opioids on the illicit market (e.g., fentanyl analogues, including carfentanil) have dramatically increased in recent years.[4-8] In 2015, about 2% of Canadians over 15 years old who used opioids reported non-medical opioid use (i.e., 83,000 Canadians).[9] Among marginalized populations (e.g., street-involved drug users, correctional inmates, First Nations/Indigenous peoples), prescription opioids (POs) have been among the most commonly used drugs for more than a decade.[10-12] Opioid-related mortality rates are escalating at alarming rates relative to just five years ago in some Canadian provinces. Across Canada, the number of apparent opioid-related deaths in 2016 was estimated at 2458 (or 8.8 per 100,000),[13] about the same number of fatalities in 2015 caused by motor vehicle accidents and homicides combined (i.e., 1858 and 604, respectively).[14,15]

Key morbidity indicators have also increased. From 2006 - 2011, hospital stays among patients with a primary diagnosis of a mental or behavioural disorder secondary to opioid use increased by 23% nationally.[16] Canadian hospitalizations related to opioid poisoning have increased over 30%, from 9 per day in 2007-2008 to 13 per day in 2014-2015.[17] Increased rates of non-medical PO use have been accompanied by a rise in PO and heroin injection and related harms.[18-22] Injecting POs is a significant risk factor for HCV[23,24] and HIV[25-27] infections, particularly among injectors younger than 30 years old.[26,28,29] Beyond acute care, admission rates for opioid-related substance use treatment have also increased. For example, the proportion of PO-related admissions to community-based addiction treatment services in Ontario almost doubled over a ten-year period, from 10.6% in 2005-2006 to nearly 20% in 2015-2016.[10,30,31] Collectively, these data reveal the magnitude of Canada's opioid emergency, especially in comparison to other recent Canadian health emergencies, such as severe acute respiratory syndrome (SARS) in 2003 (44 deaths),[32] H1N1 in 2009 (428 deaths),[33] and Ebola in 2014 (0 deaths),[34] which resulted in less mortality, yet captured national attention and presented real or potential public health crises resulting in decisive action and interventions.

B. Rationale and Objective

Addressing this public health emergency is a complex undertaking that will require a wide range of evidence-based interventions delivered along a continuum of care. The high public profile of the issue is painfully illustrated by routine reporting of death toll and severe morbidity rates. Scale-up of evidence-based interventions and services to prevent opioid users from dying or getting severely harmed is urgently needed. Moreover, to prevent adverse outcomes from spreading further and to other settings, upstream gaps in interventions and services must be addressed. Following a structured pan-Canadian consultation process facilitated by the Canadian Research Initiative on Substance Misuse (CRISM)[35] last spring, promising emerging and ongoing interventions were identified at local and regional levels to address the opioid emergency. These consultations also identified major deficiencies in intervention options offered in service systems; some provincial/local policies were also

recognised as limiting our capacity to quickly and efficiently respond to this crisis. The **rationale** of this proposal is that a coordinated program needs to be urgently developed to promote the uptake and scale-up of evidence-based secondary prevention and treatment approaches that reach the breadth and diversity of affected populations.

Canada has the second-highest opioid prescribing rates in the world, with recent increases greater than those in the US.[36,37] It is recognized that long-term systemic overprescribing of opioids is a key (direct and indirect) factor underlying much of the current morbidity and mortality. As such, CRISM fully endorses efforts to reduce overprescribing at its source, through improved prescription monitoring, opioid prescribing guidelines and rigorously enforced standards. However, because prescribing governance rests with governmental and professional regulators (e.g. colleges of physicians and surgeons), this intervention strategy is out of scope for this application. Instead the focus of this proposal is on public health interventions and addiction treatment services. Our **objective** is to develop and conduct an implementation science program in four thematic areas that have high potential for reducing the individual and population burden of opioid use. These include: (1) scaling up public health interventions (i.e., safer consumption services and naloxone delivery); (2) optimizing opioid use disorder treatments (i.e., oral and injectable opioid pharmacotherapy); (3) improving the evidence base for withdrawal management, psychosocial and recovery-based treatment options; and (4) collaboratively developing new intervention approaches to meet the needs of high-risk target populations.

C. Population and Region-Specific Variations

This proposal's interest in developing a national implementation research program requires careful consideration of significant population and regional heterogeneity across the country – both in the profile of the target problem and in the volume and diversity of interventions offered across Canada. With respect to population variability, a life course perspective indicates that youth and young adults are at particularly high risk for adverse health outcomes, given that non-medical use of prescription drugs typically begins during late adolescence or young adulthood.[10,38] Recent national data confirm elevated opioid use rates among youth relative to older Canadians, with 6% of youth aged 15 to 19 years in 2013 and 3% of Canadian youth from grades 7 to 12 in 2014-2015 reporting non-medical opioid pain reliever use.[39] Early initiation of non-medical PO use is associated with elevated risk for transitioning to injection drug use and heroin use.[18-22] Previously reported to be rare,[40,41] pharmaceutical opioid injection is currently increasing among younger persons with OUD admitted to addiction treatment.[42,43] Among patients receiving opioid agonist treatments (OAT), there is an inverse relationship between age of onset and risk of developing physical and psychiatric comorbidities in addition to OUD.[44] However, young PO users not yet linked to care may be difficult to reach, and have poor knowledge of opioid overdose avoidance and response strategies.[45,46]

Another population where risks and harms have been highly elevated – particularly in remote, rural contexts – are First Nations/Indigenous (FNI) communities. In Canada,[47,48] as in the US[49] and Australia,[50] rates of opioid use, OUD, and associated mortality and morbidity are higher among FNI peoples, compared to the general population. FNI communities have been disproportionately affected by the opioid emergency, particularly among youth and young adults, as well as young mothers. In some Northern Ontario communities, for example, over

40% of the population meet criteria for opioid dependence,[51] and rates of opioid-related harms for newborns and children (e.g., neonatal abstinence syndrome) have increased substantially. Although beneficial effects of OAT are similar in Indigenous and non-Indigenous populations,[52-54] vast discrepancies in treatment availability and access exist: OAT is presently not feasible in many First Nations communities due to unavailability of opioid agonist prescribers, and accessible pharmacies.[55] Moreover, heterogeneous community views exist about the value of medication-assisted treatment, and some Indigenous peoples experience stigma when attending OAT programs.[56] Indigenous communities also report a broad range of values and goals with respect to acceptability of public health interventions, such as syringe distribution.[57]

A further high-risk population includes people involved in correctional systems. Some 30% - 70% of (federal and provincial) correctional inmates in Canada report an illicit drug use history, with a large proportion continuing risky substance use while incarcerated.[58] Studies have demonstrated substantial increases in prescription opioid use among correctional inmates in Canada.[59] While there has been an increase in prevention and treatment (e.g., OAT) availability and initiation in Canadian correctional institutions, the correctional ombudsman for the federal prison system recently declared that demand for OAT among inmates outstrips supply.[60] In addition, both morbidity and mortality (e.g., overdose) among correctional inmates, and especially inmates released into the community is extremely high and constitutes a primary challenge for implementing effective intervention strategies.[61]

On a regional basis, opioid-related mortality and morbidity is currently greatest among the western Canadian Provinces. In British Columbia (B.C.), there were 967 illicit drug overdose (OD) deaths in 2016, an 87% increase from 2015, many related to opioids.[62] Alberta also experienced a spike in OD deaths in 2016, with 343 fentanyl-related deaths, up fivefold from 66 in 2013.[63,64] In contrast, the absolute number of reported opioid-related deaths in Québec has remained lower than in other provinces,[7,65] even as they have been increasing by about 10% annually between 2000 and 2009.[65] In the Atlantic provinces, the 2016 rate of apparent opioid-related deaths is estimated to be lower than 5 per 100,000 people for New Brunswick and Newfoundland/Labrador and within the national average (between 5 and 10 per 100,000 people) for Nova Scotia and Prince-Edward Island.[13] Morbidity rates also vary across provinces and territories, with as many as 21 opioid-related hospitalizations per 100,000 people in Saskatchewan compared to 10 per 100,000 people in Québec for 2014-2015.[17]

D. Intervention Strategies

Public Health Interventions

Extensive international evidence demonstrates that a variety of public health interventions reduce opioid-related mortality and morbidity.[66-68] Unfortunately, Canadian provinces and territories differ dramatically in their policy support for implementing them.[69] This variability underlies an inconsistent patchwork of secondary prevention and public health services across the country and inequitable access to these interventions among people who use opioids.[70] For example, Supervised Consumption Services (SCS) intervention programs to date have been implemented only in B.C.; in addition, community-driven SCS have emerged in B.C. outside of federal oversight. SCS programs have been proposed and are being developed under new legislation in Alberta, Ontario and Quebec, but are far less developed in other regions. Availability of naloxone also differs substantially between provinces, and by far the

highest rates of OAT availability and utilization have existed in Ontario and B.C., and to some extent, Quebec; in most of the other provinces, OAT systems and availability are much more limited or even under-developed.[71] Across Canada, OAT access and availability is much greater in urban as opposed to rural areas.

Supervised consumption services (SCS). Also known as 'safer injection facilities', SCS provide hygienic environments in which people who inject drugs can inject illegal drugs under the supervision of a health care professional. Numerous studies from different countries – including extensive evidence from North America's first SCS in Vancouver – have demonstrated the positive impact of SCS use and on mortality, morbidity, risk outcomes, treatment engagement, ambulance service use, and public disorder.[72]

Naloxone distribution. Naloxone distribution programs are an emergency measure to prevent/revert opioid-related overdose deaths, based on timely provision of the opioid-antidote naloxone. A recent systematic review concluded that peers can and will use naloxone to reverse ODs when properly trained, and that this training can be accomplished successfully in community-based OD prevention programs.[73] A more recent systematic review[74] of take-home naloxone (THN) programs concluded that this intervention approach reduced fatal overdoses among drug users and in the wider community, with low rates of adverse events.

Treatment Services

International evidence indicates that participating in evidence-based addiction treatment programs can also improve opioid-related health outcomes.[66,75-78] However, there is tremendous variability across Canada in accessibility of treatment programs to opioid users. Moreover, there are persistent implementation issues regarding the interface between addiction medicine programs that routinely offer opioid agonist treatments (OATs) and more traditional addiction services (detoxification, recovery programs), which typically prioritize abstinence and psychosocial intervention strategies over OAT.

Opioid Agonist Treatments (OAT). Among individuals with opioid use disorder (OUD), OAT are an effective approach to supporting abstinence from illegal or non-medical opioid use, and significantly reduce morbidity and mortality.[79] Two opioid agonist medications are currently approved for the treatment of OUD in Canada: methadone and buprenorphine/naloxone. However, these medications are largely underutilized and access is grossly inadequate in many Canadian regions.[71] Barriers include inadequate training and education of healthcare providers in evidence-based addiction medicine, and regulatory requirements for prescribing these medications. CRISM is currently developing Canada's first national clinical guideline for the treatment of OUD. Although this is an important step in promoting evidence-based treatments and consistency in clinical practice, many implementation challenges remain. For example, rapid scale-up of the number of care providers including primary care physicians and nurse practitioners trained in evidence-based opioid addiction care is needed, as well as innovative, flexible training models in order to better engage clinicians in remote and rural areas and Indigenous communities.

While buprenorphine/naloxone and methadone are preferred first-line pharmacotherapies, these medications are not suitable for all and a substantial proportion of patients are not retained on them. Alternative treatments such as slow release oral morphine and injectable hydromorphone and/or diacetylmorphine appear safe and effective for

subgroups of patients with severe, treatment-refractory OUD.[80-82] This subpopulation of people with OUD tends to be highly marginalized, experiences the highest risk of harms among opioid users, and tends to incur higher costs to the healthcare system and society. In areas where there is substantial need (i.e., high numbers of patients who have been unsuccessful with methadone), access to slow release oral morphine and injectable OAT (iOAT) needs to be scaled up. Based on evidence, these should be part of the continuum of care in the treatment of OUD. However, iOAT presents distinct barriers for implementation, including elevated requirements for treatment clinical infrastructure, and higher service delivery costs compared to methadone or buprenorphine/naloxone-based OAT delivery, which can be broadly and efficiently delivered using community-based delivery models via general practitioners and nurse practitioners.

Withdrawal management and recovery services. A range of studies have demonstrated that greater than 80% of individuals with OUD are likely to relapse to opioid use soon after withdrawal from opioids.[61,83-87] Studies have also shown that withdrawal management, when administered without linkage to long-term addiction treatment and care including OAT, is associated with elevated risk of relapse, HIV and hepatitis C transmission, and death from drug overdose.[61,83-85] Of particular concern is the loss of tolerance to opioids which may make individuals particularly susceptible to fatal overdose when relapse occurs.[61,85] Despite this, substance use treatment has largely relied on detoxification via inpatient and outpatient withdrawal management services in many Canadian jurisdictions. As with acute withdrawal management, another common practice in Canada is to place individuals with OUD in residential addiction treatment services that do not offer OAT. While little data are available on the impact of these programs, observational cohort studies have found that relapse to non-medical opioid use is relatively common following residential treatment, with reported relapse rates ranging from 60-90%.[86,87] Further, among residential treatment programs that do not include OAT, loss of tolerance coupled with high rates of relapse places individuals at increased risk of overdose, as evidenced by a national cohort study based in England that found that risk of fatal overdose was twice as high among individuals who completed abstinence-based residential treatment compared to individuals who had received OAT.[88] To address these concerns, knowledge mobilization and implementation research is required to examine withdrawal management practices and residential recovery services, document safe and efficient practices, and intervene through information exchange in order to reduce risk of fatal overdose.

E. Overview of Program Themes

As previously stated, the objective of this proposal is to develop and conduct an implementation science program in four thematic areas that have high potential for reducing the individual and population burden of opioid use. Implementation research refers to "…methods to promote the systematic uptake of proven clinical treatments, practices, organizational, and management interventions into routine practice, and hence to improve health".[89] A *Consolidated Framework for Implementation Research (CIFAR)* has been proposed for substance use disorder treatment,[90,91] according to which uptake and spread of efficacious and effective interventions are influenced by five domains: (a) intervention characteristics, (b) the outer setting or context within which organizations deliver interventions (e.g., patient needs and resources), (c) the inner setting or organizational factors related to service delivery

(e.g., structural characteristics, communication, readiness), (d) characteristics of the individuals involved, and (e) the implementation process involved. Table 1, following, outlines the proposed program themes, sub-topics of interest within them, scope, and maps the research program themes onto CIFAR domains.

Note to Readers

The implementation research themes described in Table 1, following, were developed as priority areas for the proposed program. Because of the very short timeline set by CIHR for response to the current RFA, and with their approval, the current proposal was developed largely by the CRISM NPIs, relying on select consultation with CRISM members. The text accompanying Table 1 describes these themes in relation to the overall rationale for each area as well as key implementation research priorities, but does not provide detailed descriptions of specific projects or study protocols. Acceptability of this level of detail can be confirmed by the grants facilitation staff at CIHR if necessary. Accordingly, Section E, following, describes CRISM-based structures and processes that will be used to develop and approve detailed project protocols addressing the broad research priorities described within each implementation research theme.

Table 1. Overview of implementation research themes to be developed

Theme	Sub-topics	Scope	CIFAR Domains
1. Scaling up public health interventions	• Supervised consumption and safer injection facilities: Implementation and coverage • Peer-facilitated naloxone distribution	• National • Nodes	• Intervention characteristics • Process of implementing services
2. Optimizing opioid use disorder treatments	• Addressing barriers to first line therapy and SROM • Injectable OAT: Guidance and evaluation models • Validating alternate delivery models to expand service reach, including peer involvement	• Nodes (BC and Quebec/Maritimes) • Nodes (BC and Quebec/Maritimes) • Nodes	• Intervention characteristics • Process of implementing services • Organizational context of service delivery
3. Improving the evidence base for withdrawal management, psychosocial and recovery-based treatment options	• Withdrawal management strategies • Organizational barriers to adopting public health interventions and OAT in traditional psychosocial and recovery-based programming	• National • Nodes	• Intervention characteristics • Organizational context of service delivery (e.g., patient needs and resources)
4. Developing new intervention approaches to meet the needs of high-risk target populations	• At risk youth/newer users: Targeted prevention • Indigenous peoples: Acceptability and community owndership in secondary prevention and OAT; novel interventions to improve OAT access • Corrections populations: Tailoring OAT and harm reduction to post-release needs	• Nodes • National (provisional) • National (provisional)	• Intervention characteristics • Process of implementing services • Organizational context of service delivery (e.g., patient needs and resources)

Theme 1: Scaling up public health interventions

Rationale. Policy changes and service innovations at local and regional levels are facilitating rapid expansion of public health interventions related to opioid use.[92] For example, recent federal regulatory changes have supported expansion of SCS to Montreal (2 sites), implementation is forthcoming or at an advanced stage in Toronto, Ottawa, and Edmonton, and many other Canadian cities are initiating planning processes to develop SCS. Although availability and utilization is concentrated in urban areas and is thus limited on a population basis, expanded SCS offers an opportunity to describe different implementation and delivery models and determinants of SCS utilization in relation to health outcomes, therefore providing evidence-based support for scale-up.. Naloxone distribution is evolving in a similar way across Canada; although only 7 of 13 Provinces and territories as of 2016 had THN programs,[93] federal and provincial legislation have recently been established or modified to expand naloxone distribution, and a variety of different naloxone distribution models have been proposed or implemented in different jurisdictions (e.g., injection/nasal; provision through first responders, peers, take-home programs). As with SCS, this provides a unique opportunity to support scale-up by documenting components of successful naloxone distribution programs in diverse settings, to identify modifiable barriers to uptake, and to develop harmonized service implementation measures across programs. Obtaining these results will help inform providers and stakeholders of best practices in implementing these interventions while providing insights on factors that should be adapted to their local context.

Research priorities. Expanded SCS and naloxone distribution programs will bring different implementation and delivery models in different parts of Canada, varied determinants of utilization, and variable impacts on health outcomes. From the perspective of this implementation research theme, reducing mortality and morbidity outcomes depends on identifying programs that most successfully expand reach of these evidence-based public health interventions into opioid-using populations, and supporting their uptake in new service settings. CRISM projects in this theme will therefore prioritize rapid engagement with local settings currently implementing or running SCS and naloxone distribution programs. Within CRISM Nodes, partners will identify programs, initiatives, and local innovations to be included. The process will be flexible and adaptive, to recruit ongoing and emerging services and to facilitate knowledge exchange among intervention providers, with an eye toward developing national consensus on (a) a core battery of measures assessing intervention characteristics and implementation processes, and (b) assessing the reach of programming into target populations. Key service indicators will be identified to assess characteristics of populations and programs, service delivery contexts, and implementation processes, attempting to maximize overlap with measures recommended by the NIH PhenX toolkit[94] and other large addiction studies. Developing a core set of indicators for these public health intervention programs, assessed with the same validated measurement has the potential to drastically improve research efficiency, facilitate data sharing, analyses and maximize impact for translation into policies and practice**.** Whenever possible, we will also document implementation facilitators and barriers, including regulatory standards regarding service access, extent to which peers are involved in service delivery, and efforts to tailor programs to the psychosocial needs of heterogeneous populations using opioids.

Theme 2: Optimizing opioid use disorder treatments

Rationale. In both Vancouver and Montreal, low-threshold OAT is provided to high concentrations of disenfranchised and vulnerable populations of opioid users through several low-threshold clinics that are tailored for vulnerable and hard-to-reach populations (e.g. expanded opening hours, drop-in services, on-site primary care, and syringe distribution). Conversely, in many other jurisdictions in Canada, first-line OAT medications (methadone and buprenorphine/naloxone) are not available due to regulatory challenges, leading to gaps in access. When OAT is available, there are often long wait times and available treatment options are often limited to methadone. Moreover, uptake of buprenorphine/naloxone has lagged behind methadone, despite its superior safety profile and compatibility with patient autonomy and patient-centered care.[95] Finally, universal rapid access to OAT for those in high needs settings (e.g. emergency departments, withdrawal management programs) is needed. Implementation research is thus required to improve availability of a broader range of oral OAT options to different areas of Canada. The forthcoming CRISM national opioid use disorder treatment guideline recommends buprenorphine/naloxone as a first-line treatment, followed by methadone and SROM. To support uptake, collaboration with local colleges of physicians and surgeons, health authorities, and other bodies is necessary, but most physicians do not receive training to provide OAT. Furthermore, although buprenorphine/naloxone can be prescribed without a federal exemption, pharmacological treatments for substance use disorders are seldom integrated into primary care practices. In addition to increasing access through general practitioners, initiatives in a range of Canadian jurisdictions are underway to add OAT to nurse practitioner training and practice. These emerging service models provide opportunities to examine their impact and share knowledge regarding how to implement these delivery options nationally. Beyond first-line OAT, in Vancouver, Montreal and other Canadian cities, there are emerging initiatives to implement and scale up alternative treatment options, including low threshold SROM and iOAT. In Vancouver, following the completion of the successful NAOMI and SALOME heroin prescription clinical trials,[96,97] access to iOAT has continued and is expanding. Small scale pilot programs have emerged with physicians prescribing iOAT which is then dispensed and supervised by community clinics or pharmacies. Additionally, access to iOAT will begin soon in a Montreal clinic. These initiatives provide timely opportunities to document best practices in these innovative OATs. Finally, patients and people who use drugs should be involved in the design and delivery of treatment in order to better engage and retain patients. Unfortunately, to date peers have only been included to a limited extent in the delivery of OAT. Implementation research is required to document best practices and evaluation of engagement of peer groups in service delivery.

Research priorities. In relation to this implementation research theme, reducing mortality and morbidity outcomes depends on (a) scaling up access, uptake, and engagement in first-line OATs for people with OUD, (b) efficiently triaging people with OUD who do not benefit from first-line treatments into innovative alternative treatment options such as iOAT, and more broadly, (c) identifying programs that most successfully engage peers to expand service reach. CRISM projects in this theme will therefore prioritize local settings currently implementing or running innovative OAT services, with an eye toward developing national consensus on a core battery of measures to facilitate research and outcome evaluation. We

propose to document and disseminate best practices for first and second-line OAT services by quickly engaging with relevant providers. Existing evaluation and process improvement frameworks such as the NIATx model[98] will be reviewed and adapted to the Canadian context in order to identify service and program characteristics that successfully expand access and reduce gaps in care and to promote these in other jurisdictions. In addition, CRISM will support the further expansion of iOAT through dissemination of a guidance document based on a framework developed by the BC CRISM Node. As was the case for the secondary prevention/public health interventions described above, CRISM is in a unique position to quickly conduct implementation research designed to reach national consensus on common measures and outcomes for OAT. Montreal and Vancouver have different drug epidemics, health care delivery systems and contexts. This two-node research initiative will inform future policies by identifying characteristics of populations and programs that can be utilized to scale-up treatment in other settings, while contrasting differences in environments.

Theme 3: Improving the evidence base for withdrawal management, psychosocial and recovery-based treatment options

Rationale. In many withdrawal management programs across Canada, patients are rapidly tapered off of opioids without linkage to OAT or follow-up care. This practice puts patients at risk of relapse, overdose, and infection due to injection drug use.[85,99] Further, many Canadians seek treatment for OUD in residential recovery programs, where pharmacotherapies such as OAT are often inaccessible. Some studies have found that upon discharge, clients face a heightened risk of relapse and overdose, although most recovery programs have not been comprehensively evaluated.[86-88] Therefore, best practices for safe and effective treatment within withdrawal management and recovery services need to be identified through systematic evaluations of current practices and long-term outcomes, combined with the existing evidence base in the scientific literature. Implementation research is required to intervene through information exchange and evaluation to promote safer withdrawal management and addiction treatment practices. These interventions would include ensuring patients are aware of the availability of OAT, especially when patients experience intolerable cravings and risk of relapse, and information campaigns in residential treatment facilities to modify unsafe practices, such as mandatory opioid withdrawals to qualify for admission. More broadly, implementation research is required to address controversies in the literature regarding the appropriate role of psychosocial treatment and support interventions in the treatment of OUD.[100]

Research priorities. In relation to this implementation research theme, reducing mortality and morbidity outcomes depends on engaging traditional abstinence-based addiction treatment services and clientele to <u>(a) enhance uptake of best practices in withdrawal management, and (b) promote acceptability and implementation of public health interventions and OATs as components of psychosocial treatments and in recovery programming</u>. A systematic scoping review on the role of non-pharmacological interventions in the treatment of OUD is already underway by the CRISM network. Building on this review, and in collaboration with regional service providers who do and do not offer OAT, CRISM projects in this theme will prioritize identification of key indicators and variables to describe the nature of withdrawal management, recovery, and psychosocial intervention programs for clients presenting with

opioid problems. Working with local treatment providers, we will comprehensively describe characteristics of their clientele, external and internal environments, services offered, and service flow, as well as health outcomes. Following a thorough review and examination, characteristics associated with successful treatment and long-term outcomes will be described. An integrated knowledge translation strategy will be developed to disseminate best practices to services and programs throughout Canada. Implementation research projects will be focused on select regions/cities with the greatest potential for impact and will document the extent to which best practices are being followed, identify barriers to implementation, and develop strategies to address those barriers.

Theme 4. Developing New Intervention Approaches to Meet the Needs of High-Risk Target Populations

Rationale. There is a relatively limited evidence base in Canada regarding opioid user service needs and preferences. Much of what we know derives from marginalized heroin users located in specific urban settings[12,101] As reviewed earlier, mortality, morbidity, and service coverage is distributed heterogeneously in Canada in relation to population and region. Developing innovative needs-based intervention options will require diverse approaches depending on the specific implementation research issues identified for each target population. For youth and those who have recently initiated opioid misuse, while research suggests that young PO users have poor knowledge of opioid overdose avoidance and response strategies,[45,46] little is known about their preferences for accessing relevant information and services, risks for engaging in harmful behaviours, or interventions to reduce those, including initiation of injecting. For Indigenous peoples, acceptability, community involvement, and ownership are significant barriers for implementing evidence-based public health interventions and treatment services. How these strategies coordinate with traditional knowledges and practices is not well investigated. Finally, for opioid users involved in corrections systems, efforts to identify and implement feasible interventions to increase effective service transition, and reduce overdose risk among inmates with OUD to be released into the community are needed.

Research priorities. For this implementation research theme, reducing mortality and morbidity outcomes requires focused research to (a) more adequately describe intervention needs, preferences, and psychosocial correlates of care-seeking among high-risk target populations, in order to (b) develop new approaches to expand the reach of public health interventions and treatment services. Strategically, a longer-term developmental process will be needed to address these priorities, with significant preparation and groundwork with higher risk target populations and system stakeholders. In corrections populations, for example, CRISM must negotiate a research arrangement with Correctional Services Canada to jointly identify and implement feasible interventions to increase effective service transition, and reduce overdose risk, among a sub-set of inmates with OUD (e.g., a cohort from select institutions/regions) to be released into the community. Feasibility assessment is required to determine the viability of implementation research targeting cognitive-behavioral or educational interventions pre-release, improved service/transition plan developments, and/or naloxone provision upon release can be described. Similarly, developing respectful and trusting

working relationships with Indigenous communities requires CRISM to participate in a variety of cultural protocols with a variety of stakeholders. Development of protocols to ensure community ownership over research processes designed to better meet the needs of these communities is expected. In addition to these longer-term approaches, CRISM will also work opportunistically to identify projects already ongoing or being implemented that could benefit from the research program. Examples of such projects include (a) implementation of naloxone training in the Onento'Kon Healing lodge inpatient therapy, for opioid users initiating buprenorphine/naloxone (this facility is treating Indigenous peoples including many from remote regions in Canada), and (b) implementation of targeted prevention interventions among high-risk youth in diverse settings (e.g., drug testing at music festivals; targeted prevention among high risk students in schools).

F. Program Development Process

The proposed research program will include a mix of local, regional and national projects, integrated to maximize generalizability of information and results, and will be combined with an iterative process for knowledge exchange with communities and policy makers. As a new national and regional research-practice network, CRISM's intention is to use the process of identifying and developing protocols for specific projects within the implementation research themes proposed in Table 1 as an opportunity to engage CRISM members. Projects will be carefully chosen to inform implementation and scale-up of successful interventions across Canada. Thus, the program development process is designed to allow members to declare their interests in specified implementation research areas, assemble regional and national teams of interested researchers, practitioners, and decision-makers to formulate specific projects within those areas, and collaborate in knowledge exchange within and beyond the CRISM Network.

Collaborative Principles

Activities across the proposed program will be developed to ensure meaningful engagement of people with lived experience of opioid problems (note that CRISM defines this inclusively, i.e., drug user as well as recovery communities) and Indigenous peoples, as outlined in the following subsections.

Peer involvement. CRISM recognizes the need to empower people with lived experience of opioid problems to make meaningful contributions to the proposed research program, and supports "nothing about us without us", the guiding principle of the Canadian Association of People Who Use Drugs (CAPUD). CRISM has already begun to formalize opportunities for peer advocacy groups to be involved in the network, with efforts underway and support being provided to CAPUD, Alberta Addicts Who Educate and Advocate Responsibly (AAWEAR), the Vancouver Area Network of Drug Users (VANDU), and others. Research program development will require project teams to institutionalize involvement of people with lived experience as part of governance and operational decision making. Beyond governance, several of the specific implementation research topics identified in Table 1 emphasize peers as an integral component of intervention strategies to be investigated (i.e., peer-facilitated naloxone distribution, alternate delivery models for OAT).

Working with Indigenous peoples. CRISM joins others across Canada in recognizing the deleterious effects of historical practices of cultural suppression and forced assimilation of Indigenous peoples. Building on the strengths-based work of several CIHR and Health Canada-funded initiatives, CRISM will therefore prioritize engagement and partnerships with Indigenous populations as a foundational implementation research principle. Through the expertise of Indigenous knowledge brokers and research team members we will engage a two-eyed seeing approach, the requisite guiding principle for integrative sciences. Two-eyed seeing, a model proposed by Mi'kmaq Elders Albert and Murdena Marshal, draws on the strengths of Indigenous and Euro-Western worldviews to foster knowledge building, collaboration, and understanding to benefit research and health outcomes. Complementing the two-eyed seeing approach,[102] CRISM implementation research with this population will adhere to the principles expressed in the Honouring Our Strengths (HOS) Renewal Framework.[103] The HOS framework outlines a six-point continuum of care for individuals, families, and communities to address substance use issues that are specific to Indigenous communities. The continuum of care is fostered by adherence to ten guiding principles that include; shared-responsibility, connection, respect, balance, culturally competent and safe care, holistic support, resilience-focused, community-focused, and spirit-centred approaches. These principles also provide foundational elements for building strong research relationships and future partnerships between Elders, Knowledge Keepers, Indigenous-led organizations, and the CRISM network. Operationally, we anticipate that specific projects with Indigenous communities will be handed off and owned by community representatives, who will work closely with researchers with relevant expertise and credibility to implement these principles.

Project Development: Processes and Timelines

The following processes and timelines will be used to develop the proposed implementation research program:

1. Program funding will be allocated equitably across the four CRISM Nodes, as per the CRISM governance statement submitted to CIHR (this process to be completed during 2017-Q3);
2. Post-funding, declarations of interest in the four implementation research theme areas described in Table 1 will be solicited from CRISM regional members by the CRISM Nominated Principal Investigators (NPIs) using a structured process, standardized across Nodes (to be completed during 2017-Q4);
3. Provisional teams will be formed for each theme area by organizing expressions of interest. The NPI group will facilitate a collaborative review process, bringing together provisional team members in each research theme area in order to (a) clarify specific interests of investigators and system stakeholders in the theme area, (b) identify existing research activities and service innovations that could be quickly turned into program projects, (c) brainstorm about longer-term strategic development of projects for the theme area, (d) discuss theme area leadership, and (e) formulate a priority list of projects within the theme area (to be completed during 2018-Q1);
4. A lead CRISM Node will be identified to take primary responsibility for the development of projects within each theme area, drawing on the broader membership with interests in this

area across the national network (to be completed during 2018-Q1);

5. A qualified PI or project manager for the lead node(s) will be identified to provide oversight, leadership, and coordination of projects within each theme area (to be completed during 2018-Q1);
6. Lead Nodes and PIs will produce a work plan for the research area. Project work plans will be reviewed and approved by the NPIs and subsequently by the CRISM National Executive Committee. Projects within each of the proposed theme areas will be required to form a reference group including CRISM investigators, service providers, stakeholders, affected population and communities from multiple CRISM nodes, to develop a comprehensive knowledge exchange plan for communicating results to stakeholder communities (to be completed during 2018-Q1);
7. Following approval of work plans, project funding will flow to the institution of the lead CRISM Node and project PI via subcontract (to be completed during 2018-Q1);
8. Projects comprising the program will begin in 2018-Q2).

G. The Applicants

The Canadian Research Initiative in Substance Misuse (CRISM) is a national network of over 500 substance use researchers, service providers, decision makers, and people with lived experience. CRISM's overall aim is to translate evidence-based interventions for substance use into clinical practice, community-based prevention, harm reduction, and health system changes. Funded by the Canadian Institutes of Health Research (CIHR), CRISM consists of four large interdisciplinary regional teams, with network hubs based in Vancouver, Edmonton, Toronto, and Montreal, referred to individually as Nodes and collectively as the Network.

The CRISM Network has been mandated to (1) identify and/or develop the most appropriate and effective clinical and community-based treatment and prevention interventions for substance misuse and addictions; (2) provide evidence to enhance treatment and prevention services among service providers and decision-makers; and (3) support efforts to improve quality of care and quality of life for Canadians living with substance misuse or addictions. CRISM has prioritized these objectives since its inception in late 2015, and has also provided evidence-based input to regulatory/policy change. Meaningful engagement, knowledge transfer and exchange, and network reach are key operating principles within these mandates.

Leadership

The collective expertise of CRISM encompasses the full spectrum of opioid systems of care and includes expertise and in-depth knowledge of research methodologies, the landscape of health care delivery structures and opportunities for improvement, and regional variation in health regulations and policies. From the Atlantic to Pacific coasts, the nodes are led by four Nominated Principal Investigators (NPIs), including: Drs Julie Bruneau, Benedikt Fischer, Cameron Wild, and Evan Wood. Dr. Bruneau is Head of Primary Care Medicine at the University of Montreal affiliated hospital (CHUM), is recognized as a leader in addiction medicine in Canada, and was central in the development of provincial OAT and syringe distribution program

networks in Quebec. Dr. Fischer is an international leader in his fields of research on illicit and prescription drug use, with emphasis on knowledge translation, epidemiology, prevention, intervention, and policy development. Dr. Wild specializes in psychosocial aspects of addiction treatment and prevention, and is recognized for his work on using evidence about population needs to inform systems of care. Dr. Wood is an addiction medicine physician and epidemiologist, and a recognized leader in substance use research, education and clinical care, and community-based interventions for HIV and substance use. Collectively, the four CRISM Nominated Principal Investigators have decades of research and project management experience, and have published 1071 peer-reviewed research articles as of this application.

Membership and Expertise

Due to longstanding historical barriers in Canada regarding uptake of evidence-based practices, interventions, and policies in the addiction area, CRISM is appropriately viewed as an implementation science research-practice network. CRISM defines expertise in this area inclusively, i.e., Node member-researchers with interests in this area as well as non-academic CRISM members who (a) currently participate in Node implementation research projects, or (b) who can be mobilized to support future implementation research projects.

The CRISM network currently includes over 270 member-researchers with expertise in addiction medicine, epidemiology, clinical research in addiction psychiatry, research on community-based psychosocial, and clinical interventions for substance abuse and related co-morbidities, withdrawal management processes, and program development for prevention and treatment. CRISM member-researchers have made significant impacts in the implementation of substance use interventions. These include the development and dissemination of educational, diagnostic, and other resources, development of training programs for healthcare providers, evaluation of supervised injection services, implementation of public health and overdose prevention services, and feasibility studies to integrate new substance use interventions into existing healthcare settings. CRISM researchers have longstanding collaborations and working relationships with marginalized substance use communities, Indigenous communities, and at-risk youth in many Canadian cities and regions. In addition to research expertise, the CRISM membership encompasses over 200 non-academic partners, including 59 policy makers and regulatory officials at the regional/provincial level, over 115 direct service providers, and over 49 people with lived experience from across Canada. With decades of experience, the CRISM Nodes have on-the-ground capacity to implement innovative research, collaborate with health system partners to spread and scale-up evidence-based interventions, and effectively translate knowledge into policy change. No other research-practice network in Canada has the national span, depth of experience, and rapid mobility that CRISM embodies.

Research Infrastructure

The CRISM Research Infrastructure (RI) includes facilities, resources, and related services made available at numerous academic and clinical institutions including: Dalhousie University, University of Montreal Research Center, Ontario's Centre for Addiction and Mental Health (an academic care, training and research centre affiliated with U of Toronto), the Universities of

Alberta, Calgary, Lethbridge, Manitoba and Saskatchewan, University of British Columbia, the British Columbia Center for Excellence in HIV/AIDS, and most recently the British Columbia Center for Substance Use. Each Node has developed RI to support current (e.g., OPTIMA trial, see next subsection) and future projects. This growing infrastructure includes: research space; facilities for subject recruitment, randomization and clinical/non-clinical assessments; medication storage/dispensing and data collection, storage and analysis capacity (both computing and personnel), singular large-scale and small-scale research installations, databases, libraries, high capacity communication networks, access to bioinformatics, biostatistics expertise, scientific and medical writing platforms and infrastructural centers of competence.

The CRISM Nodes have created websites (https://crismprairies.ca/; http://crismontario.ca/; http://qmcrism-icras.ca/; http://www.bccsu.ca/about-crism-bc/) to facilitate information exchange and communication with their members, stakeholders and each other. Information that is shared on the websites includes regional and national data associated with drug use across Canada, as well as research evidence (including prevention, harm reduction and specialty addiction treatment). To date, CRISM RI has facilitated the publication and dissemination of the National Lower Risk Cannabis Use Guidelines[104] in a timely manner (in June 2017), the upcoming publication and dissemination of a National Guideline for the Clinical Management of Opioid Use Disorder, as well as development and implementation of the OPTIMA Trial, and a wide range of regional research projects and trials. Teams of dedicated and qualified scientists, research professionals and trainees are instrumental to this research infrastructure. The CRISM RI serves facilitates meaningful engagement, knowledge transfer, education and sustainability.

Current Opioid-Related Work

CRISM leaders and Node members have conducted the bulk of Canadian research on opioids, and have made significant contributions to epidemiology, prevention and treatment programs, and policy analysis.[24,31,36,77,105-120] This foundation has facilitated development of several CRISM-led initiatives in the area.

OPTIMA. Although methadone has long been the standard of care for treatment of opioid use disorder in Canada, there is growing consensus that the superior safety profile of buprenorphine/naloxone, as well as other comparative advantages, supports its use as a first-line therapy for opioid use disorder. The CRISM Network has been funded via CIHR to conduct a national study to evaluate these two treatment options in order to generate evidence directly addresses a recognized national public health priority. The trial is called *OPTIMA (Optimizing Patient Centered-care: A Pragmatic Randomized Controlled Trial Comparing Models of Care in the Management of Prescription Opioid Misuse).* OPTIMA is an open-label randomized pragmatic trial designed to compare methadone versus buprenorphine/naloxone-based models of care and will generate practice-based evidence relevant for front-line service providers. Study protocols, ancillary studies, main trial staff recruitment and training, as well as ethical and administrative approvals have been finalized, and OPTIMA will begin enrollment in late Summer, 2017.

Knowledge transfer and exchange. Complementing the OPTIMA trial, CRISM is

engaging in opioid-related knowledge transfer activities. In recent months, there has been increased public concern on the emerging health crisis relating to opioid misuse. The CRISM leads were approached by the Federal Minister of Health to create a clinical guideline on opioid use disorder for nationwide dissemination and implementation. CRISM convened a national panel of 40 clinical leaders from across the country to review and modify BC's guideline; the network is in the final stages of producing a National Treatment Guideline, which will be a key resource for the proposed research. In addition, Health Canada has asked CRISM to conduct fieldwork with regulatory and clinical leaders across Canada regarding current policies governing methadone treatment. In light of concerns that these policies are too restrictive and should be revised to allow for a more flexible and effective opioid treatment continuum, CRISM is currently executing a systematic consultation process across the country regarding current S. 56/CDSA requirements for physicians to obtain methadone treatment exemptions. Both of these knowledge exchange projects reflect CRISM's aspiration to be a national resource for opioid-related practice and policy innovation.

H. Budget

Overview

As shown in Table 2, each of the four CRISM Nodes will receive an equal amount of $375,000.00 CAD/year over a period of 5 years, consistent with CRISM governance statement submitted to CIHR. The structured process described earlier will be used to allocate funds to carefully selected local, regional and national projects to be developed from the implementation research program themes. In addition, each CRISM Node will reserve 10% of funding to contribute to a national coordination team, as described below.

Table 2. Overview of budget

Item	Yearly cost	Total cost for funding period
BC Node	$375,000	$1,875,000
Prairies Node	$375,000	$1,875,000
Ontario Node	$375,000	$1,875,000
Quebec/Maritimes Node	$375,000	$1,875,000

Project Development – Budget Implications

As stated earlier, project development within the program is intended as an opportunity to engage CRISM members. The structured process described earlier will identify lead CRISM Nodes and lead Principal Investigators (PIs) for projects. PIs who will lead projects within the research program and who are not employees of the institutions receiving program funding will receive shared funds from Node budgets; these funds will be transferred via subcontracts to collaborating institutions, following approval of work plans and budgets. This approach will ensure that project PIs receive appropriate institutional recognition for their involvement in the program.

Funding to CRISM Nodes: $375,000 per year for Years 1 – 5: Total = $1,875,000/Node

Budgets for approved local, regional and national projects comprising this program will cover costs of:

1. research personnel and trainees who will implement approved protocols;
2. data collection;
3. data coordination, management and analytics;
4. assessment programs and tools, and intervention development;
5. contract research organisation services and expertise;
6. travel, meetings, administrative costs;
7. publications, knowledge translation/transfer and reporting;
8. other program related expenses.

All budgets submitted for program projects will comply with CIHR funding rules and requirements. The CRISM NPI group will utilize the currently-funded research infrastructure to complement proposed program funding whenever possible.

National Coordination: $150,000 per year, based on equal contributions of $37,500/Node per Year): Total = $750,000 for 5 years

Role. A total of 10% of the program budget will be allocated toward a National coordinating team dedicated to the opioid emergency. The role of this team is to (1) ensure that new projects developed within the program capitalize on, and harmonize with, existing CRISM research infrastructure; (2) work with the CRISM NPI group to operationalize outreach, consultation, and review processes that will be used to develop and approve new projects, (3) provide a single point of contact for National stakeholders regarding CRISM's implementation research program, and (4) provide support for implementing new projects, including: oversight and administrative support for subcontracting arrangements, study design, protocol development, data capture and secure warehousing, data analytics, and integrated knowledge exchange with regional and national stakeholders. These roles will be implemented by a team that includes (a) a Lead CRISM Node Principal investigator for each approved project in the program, (b) one National Program Director, and (c) one part-time program coordinator.

Principal Investigators (PIs). PIs for projects approved by the program will work closely with the National Program Director and regional CRISM project teams to oversee implementation of their projects and will be designated as project leads in CIHR subcontracts. It is expected that each project PI will donate their time to these activities (i.e., no funding will be allocated to compensate PIs for their time) and that time commitments will vary based on the project work plan and the project leadership investment expected. Additionally, in Years 4 – 5 , PIs will develop a publication plan for their projects in collaboration with the CRISM NPIs, to both lead and co-lead scientific manuscripts. They will not receive salaries for executing projects comprising the proposed program.

National Program Director. This individual (to be named) will dedicate 3.0 calendar months in Year 1 to support the process of selecting and vetting projects that comprise the program. The National Program Director will be the first recruited member of the National

coordination team for this reason. The Program Director will allocate 12 calendar months in Year 2 to support project initiation for projects. In Year 3, 9 months will allocated to support project implementation and in Years 4-5, as the projects will be well underway it is expected the time commitment to decrease to 6.0 months. In Years 4-5, it is expected that this CRISM resource will be allocated to other National research programs of the CRISM network.

Part-time Program Coordinator. This individual (to be named) will provide coordination/managerial support to the National Program Director. Time allocated to the program will vary based on the nature of the projects supported and the requirements of the National Program Director. Duties will involve preparing the elements of shared costs/ resources model used by the network to manage the program, developing project subcontracts, including amendments, changes and other actions required, and coordinating information exchange about the program within and beyond the CRISM network.

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