Canadian Take-Home Naloxone Program Guidance

NATIONAL GUIDANCE

CRISM-ICRAS
Canadian Research Initiative in Substance Misuse
Initiative Canadienne de Recherche en Abus de Substance

CIHR IRSC
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* Senior leadership responsibilities were shared equally among three principal investigators.

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Table of Contents

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We recognize the significant contributions of the 16 group members with lived and living experience of substance use who brought their expertise and experience to this project, some of whom chose to self-identify as people with lived and living experience/expertise (PWLLE) and use their own words in the affiliation section below.

Note: Some Naloxone Guidance Development Group members sat on multiple committees.

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We thank the Naloxone Guidance Development Group for their contributions to this project amid escalating drug toxicity and overdose deaths and the COVID-19 pandemic. The group contributed significant time to this project with the goal to improve harm reduction infrastructure within Canada and we are privileged to work alongside them.

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ABOUT THE CANADIAN RESEARCH INITIATIVE IN SUBSTANCE MISUSE

Funded by the Canadian Institutes of Health Research (CIHR), the Canadian Research Initiative in Substance Misuse (CRISM) is a national research consortium focused on substance use disorders, comprising five large interdisciplinary regional teams (nodes) representing British Columbia, the Prairies, Ontario, Quebec, and the Atlantic region. Each CRISM node has an expert network of research scientists, service providers, policy makers, community leaders, and people with lived and living experience of substance use. CRISM's mission is to translate the best scientific evidence into clinical practice and policy change.

NOTE: The authors acknowledge the stigmatizing nature of the term "Substance Misuse" in the CRISM name, respect the autonomy of people who use drugs, and support person-centred language.

DEFINITIONS

***Content Warning**: This section discusses physiology of overdose. We identified relevant sections in the report with blue and italicized text for anyone who may find this content distressing and would prefer to avoid it. We encourage readers to pause and reach out to supports as needed.*

Cardiac arrest: When the heart stops beating or beats too ineffectively to circulate blood to the organs (Dezfulian et al., 2021).

Community overdose responder: For the purposes of this report, a community overdose responder or community responder is someone responding to overdose outside of a health care, overdose prevention site, or emergency service role (even when they also respond to overdose in professional roles at these sites). While community responders are not exclusively people who use drugs, we know that people who use drugs comprise a significant proportion of those who respond to overdoses (Lei et al., 2022).

Community evidence: Knowledge generated from observations and experiences (Schünemann et al., 2019); here we refer to the expertise of people with lived and living experience of drug use, overdose, and overdose response.

Compression-only CPR: Cardiopulmonary resuscitation where the responder administers compressions to the middle of the chest without providing rescue breathing (Panchal et al., 2020).

Conventional CPR: At the time of publication, conventional cardiopulmonary resuscitation includes both rescue breathing and chest compressions (Panchal et al., 2020).

Person/people with lived and living experience/expertise: In this report, when we discuss people with lived and living experience/expertise, we are referring to those with self-identified experience of drug use. We use the term people with lived and living experience/expertise in recognition of the diversity of ways that people identify and the expertise of lived experience (Austin & Boyd, 2021).

***Opioid overdose**: During opioid overdose, interaction of the opioid with the cerebral μ (mu) receptors cause respiration depression leading to insufficient oxygen for the body's demands. This lack of oxygen may cause damage to the heart (which may stop beating or stop beating effectively), the brain, and other vital organs. Opioid overdose may be fatal or non-fatal, as opioid overdose may not progress beyond mild respiratory depression (slowed breathing) depending on the dose of the opioid and the individual's level of tolerance. Some people who survive overdose may experience injury or disability in different organ systems related to low levels of oxygen in the body during overdose (Dezfulian et al., 2021).*

***Overdose crisis:** An increase in loss of life caused by toxic drugs in the unregulated street supply and drug policies that contribute to acute toxicity events. A variety of terms are used to describe the crisis (such as the unregulated drug poisoning emergency, the toxic drug crisis, the poisoning crisis, and in some jurisdictions the addition crisis), due to important context-specific considerations (Beletsky & Davis, 2017). While people who use different types of drugs are affected by the overdose crisis, take-home naloxone programs are important because opioids are responsible for most of the increased toxicity in the drug supply (Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses, 2023).*

Rescue breathing: When a responder breathes into the airway of someone unable to breathe independently with the goal of providing oxygen and ventilation (Panchal et al., 2020).

Respiratory depression: When breathing slows or stops (Dezfulian et al., 2021).

EXECUTIVE SUMMARY

We developed this guidance document on take-home naloxone programs in Canada in collaboration with a Naloxone Guidance Development Group comprised of people with lived and living experience/expertise of drug use and responding to overdose, frontline overdose response and harm reduction workers, public health professionals, clinicians, and academics with expertise in harm reduction. We used an adapted Delphi method to identify questions that the Naloxone Guidance Development Group felt were important to address (Ferguson et al., 2022).

Systematic reviews on the three most important topics identified by the adapted Delphi method informed the recommendations. The research questions included:

1) Route of Administration: What is the effect of intramuscular vs intranasal naloxone administration in community setting on morbidity or mortality of persons experiencing opioid overdose?
2) Kit Contents: What is the evidence to support the impact of specific naloxone kit contents on outcomes including infection control, preference, or health outcomes? This question is framed from both the perspective of people experiencing overdose and people responding to overdose in the community setting.
3) Overdose Response: Are there different rates of mortality and morbidity for persons experiencing opioid overdose in community settings associated with various overdose responses in addition to naloxone administration: a) rescue breathing, b) conventional cardiopulmonary resuscitation (CPR) including rescue breathing, c) compression-only CPR, or d) neither rescue breathing or chest compressions?

We used the GRADE framework to determine the strength of recommendations and the quality of published academic and grey literature evidence (Schünemann et al., 2013). The quality of published evidence was very low for all systematic reviews. This low rating was due to the focus in the literature on evidence focussing on health professionals rather than evidence studying the experience of community overdose responders or taking their expertise into account. There is a lack of research that would be considered ‘high quality’ in the GRADE framework on this topic in the context of life-saving interventions. Randomized controlled trials are often not ethical or feasible in this scenario.

We recognize the expert community evidence of people who use drugs and have overdose response experience. We have incorporated this evidence throughout guidance development process.

Our recommendations are as follows:

Topic	**Recommendation**	**Strength of Recommendation**	**Quality of Published Academic and Grey Literature Evidence**
Route of Administration	Take-home naloxone programs should offer both intramuscular and intranasal formulations of naloxone, so that people accessing naloxone kits can choose their preferred formulation	Conditional	Very Low
Kit Contents	All take-home naloxone kits should include: • A recognizable carrying case • Non-latex gloves • A rescue breathing mask • Instructions on naloxone administration o Instructions on how to administer naloxone should be designed in collaboration with people who use these kits. Take-home naloxone programs can use previously developed instructions or develop their own in collaboration with the affected community Intramuscular take-home naloxone kits should include: • Three or more 0.4 mg/ml naloxone ampoules or vials based on program discretion and local experience (more ampoules or vials may be necessary in communities with high prevalence of illicitly manufactured fentanyl and other potent synthetic opioids) • A syringe and needle for each ampoule or vial of naloxone • Alcohol swabs • Ampoule breaker (in kits containing ampoules) Intranasal take-home naloxone kits should include: Two 4 mg/0.1ml intranasal devices	Strong	Very Low
Overdose Response	Response to suspected opioid overdose should depend on the skill and comfort level of the responder. People accessing services	Strong	Very Low

	at THN distribution sites may be trained on overdose response through their peers, using online resources, a cardiopulmonary resuscitation (CPR) training course, or training developed by THN programs. Trained community responders should follow these steps: • Apply vigorous verbal and physical stimuli • Call emergency medical services (EMS)[1] • Administer naloxone[2] • If the individual experiencing overdose is in respiratory depression, provide rescue breathing • If the individual experiencing overdose is in cardiac arrest, provide conventional cardiopulmonary resuscitation (CPR) including rescue breathing and chest compressions THN distribution sites without capacity to offer overdose response education should direct people to services that offer training, if needed.		

[1] We acknowledge that many people who use drugs do not feel safe calling EMS, especially in jurisdictions where police commonly attend EMS calls for overdose.
[2] There is differing guidance on the order of naloxone administration and resuscitation. Our recommendation does not address order of response interventions.

INTRODUCTION

BACKGROUND

THE OVERDOSE CRISIS

***Content Warning**: This section discusses lives lost due to the overdose crisis. We identified relevant sections in the report with blue and italicized text for anyone who may find this content distressing and would prefer to avoid it. We encourage readers to pause and reach out to supports as needed.*

A large number of people are dying of preventable deaths due to opioid overdose worldwide (CDC Injury Center, 2022; Krausz et al., 2021; World Health Organization, 2020; Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses, 2023), and particularly in North America (Krausz et al., 2021). More than 90,000 people lost their lives due to drug overdose deaths in the USA in 2020 (CDC Injury Center, 2022). Rates of opioid-specific toxicity deaths are surging. In Canada, a total of 34,455 people lost their lives because of drug toxicity between January 2016 and September 2022 (Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses, 2023). The crisis is driven by high and unpredictable levels of fentanyl and analogues in the illicit drug supply (Crabtree et al., 2020; Krausz et al., 2021; Singh et al., 2020). Of all accidental drug toxicity deaths in Canada (January to September 2022), 81% involved fentanyl (Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses, 2023).

The start of the COVID 19 pandemic changed the nature of the illicit drug supply due to a disrupted supply chain. Participants in a study of adults who use drugs from across Canada reported that the quality of drugs decreased and the cost increased, prompting some to change the drugs that they use or prompting them to use more drugs to account for decreased potency, increased mental distress, and uncertainty of future availability (Ali et al., 2021). The rate of overdose deaths rose during the COVID-19 pandemic, exacerbating an already dire situation (Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses, 2023; Gomes et al., 2021).

TAKE-HOME NALOXONE

When someone uses opioids, the opioid binds to μ (mu) opioid receptors in the brain which may cause many effects including pain relief, euphoria and slowed breathing (Dezfulian et al., 2021). Naloxone binds more effectively to the μ brain receptors, which displaces the opioids if they are present; and therefore successful administration of naloxone may reverse respiratory depression (slow or absent breathing) and can prevent cardiac arrest (when the heart stops pumping or pumps too ineffectively to support vital organs) associated with opioid overdose (Dezfulian et al., 2021). It is important to note that naloxone only reverses opioid overdoses, which includes substances like fentanyl, diacetylmorphine (heroin), and morphine and does not reverse the effects of benzodiazepines or stimulants. This is an especially important consideration since using multiple substances is common in overdose scenarios in Canada, with more than half of opioid toxicity deaths also involving a stimulant, and 41% of overdoses involving a non-opioid, non-stimulant substance between January and September 2022 (Federal, provincial, and territorial Special Advisory Committee on the Epidemic of Opioid Overdoses, 2023). The inability of naloxone to act on drugs other than opioids complicates overdose response when both opioids and benzodiazepines are used, especially considering that benzodiazepines are often an contaminant that people using these drugs may be not be aware of (Purssell et al., 2021).

Between 2012 and 2017, all provinces and territories across Canada launched publicly funded take-home naloxone (THN) programs to address increasing rates of overdose deaths (Moustaqim-Barrette et al., 2019). In Canada, wide-reaching THN programs provide kits at no cost without a prescription, so that community members can respond to overdoses (Moustaqim-Barrette et al., 2019). THN is a life-saving measure which was estimated to avert 1,580 deaths in British Columbia between January 2012 to December 2017 (Irvine et al., 2019).

People who use drugs are central to the development of harm reduction initiatives and often leverage personal knowledge and skills to provide high quality services (Marshall et al., 2015). It is important that people who use substances have access to THN kits because they are the people most often responding to overdose in the community. Among the 87,507 kits obtained in British Columbia between 2017 and 2020 to replace a kit after an overdose, 87% were collected by people who use drugs from the unregulated drug supply (Lei et al., 2022).

While THN programs are critical to the overdose crisis and overdose response, we acknowledge that naloxone alone is not sufficient to address the loss of life (BC Centre for Disease Control, 2021). People who use drugs undergo unnecessary trauma related to experiencing and responding to overdose (BC Centre for Disease Control, 2021). Other interventions, including safer supply and decriminalization initiatives, also meaningfully improve the lives of people who use drugs (BC Centre for Disease Control, 2021). Click here to read the perspectives of people who use drugs on naloxone and the impact of the overdose crisis.

Alongside the known benefits, there are some important adverse effects related to the administration of naloxone to consider when implementing THN programs. Administering higher doses of naloxone than are necessary to reverse respiratory depression can cause acute withdrawal syndrome for people who are physiologically dependent on opioids. Opioid withdrawal may include:

- extreme pain and discomfort (Bluthenthal et al., 2020),
- sweating, pain, vomiting, and agitation (Purssell et al., 2020).

In rare cases, people may experience:

- pulmonary edema (fluid collecting in the lungs) (Purssell et al., 2020; Reed & Glauser, 1991; SoumyaShankar et al., 2009; Sporer & Dorn, 2001),
- seizure (Kerr et al., 2009; Kim & Nelson, 2015),
- arrhythmias (a problem with the rate or rhythm of the heartbeat), or cardiac arrest (when the heart stops beating or beats too ineffectively to support vital organs) (Cuss et al., 1984; Wermeling, 2015).

EXISTING GUIDELINES

We searched existing evidence-informed guidance documents and found five relevant to THN. We did not identify any Canadian guidelines specific to community overdose response. Please see Table 1 for a summary of related guidelines. Our team sought to develop guidance based on current evidence, both published and from affected communities, and guidance documents, for implementation in the Canadian context.

Table 1: Existing Guidelines on Take-Home Naloxone (THN)

Citation	Date	Country	Key Conclusions
Wenger, L. D., Doe-Simkins, M., Wheeler, E., Ongais, L., Morris, T., Bluthenthal, R. N., Kral, A. H., & Lambdin, B. H. (2022). Best practices for community-based overdose education and naloxone distribution programs: Results from using the Delphi approach. *Harm Reduction Journal*, *19*(1), 55. https://doi.org/10.1186/s12954-022-00639-z	2022	USA	Best practices for community-based overdose education and naloxone distribution programs based on a modified Delphi offer 20 recommendations on topics including staff training and support, naloxone saturation and supply and culturally appropriate service, and is grounded in harm reduction (p. 5-6).
Tsuyuki, R. T., Arora, V., Barnes, M., Beazely, M. A., Boivin, M., Christofides, A., Patel, H., Laroche, J., Sihota, A., & So, R. (2020). Canadian national consensus guidelines for naloxone prescribing by pharmacists. *Canadian Pharmacists Journal / Revue Des Pharmaciens Du Canada*, *153*(6), 347–351. https://doi.org/10.1177/1715163520949973	2020	Canada	Canadian national consensus guidelines for naloxone prescribing for pharmacists include the following recommendations: ● All patients receiving an opioid should be dispensed take-home naloxone and counseled by a pharmacist (p. 349). ● Reminders should be set for pharmacies to follow up with people after 3 months and at 1 year after dispensing take-home naloxone. Ongoing yearly follow-up is recommended to ensure THN kits have not expired and to reinforce overdose prevention education (p. 349).
Jobin, N., & Rossignol, M. (2018). La réanimation cardiorespiratoire (RCR) dans le contexte de l'administration de naloxone pour surdose d'opioïdes dans la communauté (p. 78). Institut national d'excellence en santé et en services sociaux (INESSS). https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Medicaments/INESSS_Avis_naloxone_RCR.pdf	2018	Canada	The Institut national d'excellence en santé et en services sociaux released a report on best practices in the area of resuscitation measures to be recommended to the general public in circumstances of naloxone administration. Recommendations include: • A description of the sequence of resuscitation including chest compression only. • Provision of a barrier mask in THN kits for overdose responders trained in CPR. • Evaluation of intranasal naloxone as an option for Quebec naloxone distribution programs. • Development and improvement of training in naloxone administration for potential community overdose responders. • Funding for evaluation of naloxone distribution programs.
Kampman, K., Jarvis, M., & FASAM. (2015). American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of	2015	USA	The American Society of Addiction Medicine released guidelines which included the following recommendations relevant to take-home naloxone: ● Naloxone should be given in case of opioid overdose. ● Naloxone can and should be administered to

Addiction Involving Opioid Use. *Journal of Addiction Medicine*, *9*(5), 358–367. https://doi.org/10.1097/ADM.0000000000000166			pregnant women in cases of overdose to save the mother's life (p. 365).
World Health Organization, Management of Substance Abuse Team, & World Health Organization. (2014). *Community management of opioid overdose.* http://www.ncbi.nlm.nih.gov/books/NBK264311/	2014	International	The World Health Organization released guidelines which include the following recommendations: • People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose (p. x). • Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous, and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context (p. x). • In suspected opioid overdose, first responders should focus on airway management, assisting ventilation, and administering naloxone (p. x). • After successful resuscitation following the administration of naloxone, the level of consciousness and breathing of the affected person should be closely observed until full recovery has been achieved (p. x).

HOW THE GUIDANCE WAS DEVELOPED

PURPOSE AND SCOPE

The objective of the THN guidance development project is to provide recommendations for the use of the opioid antagonist naloxone for suspected opioid overdose by community responders supported by published peer-reviewed literature, relevant grey literature, guidance documents, and multidisciplinary consensus. While there remain some province and territory-specific issues related to the distribution of naloxone, such as funding and pharmacy dispensing, the guidance development project aims to address issues of national scope and support the adoption of standardized practice across Canadian provinces and territories.

The project presents the international scientific evidence base and current guidance documents supporting distribution and use of naloxone by community overdose responders for administration in out-of-hospital settings. Published academic and grey literature evidence related to the use of naloxone within a hospital context and procedures specific to emergency services (police, firefighters, paramedics, and emergency departments) may be used to inform questions, but recommendations for practice in such contexts are considered beyond the scope of this project. Additionally, this guidance does not seek to review evidence related to the identification or treatment of opioid use disorder, needle distribution programs, or supervised consumption services.

INTENDED AUDIENCE

The target audience of this guidance is those who develop, fund, and implement THN programs, including:

- Non-profit and government agencies
- Community overdose responders, harm reduction workers, public health professionals, and clinicians
- Regulatory agencies and other decision-makers

CANADIAN TAKE-HOME NALOXONE PROGRAM GUIDANCE PROJECT OVERVIEW

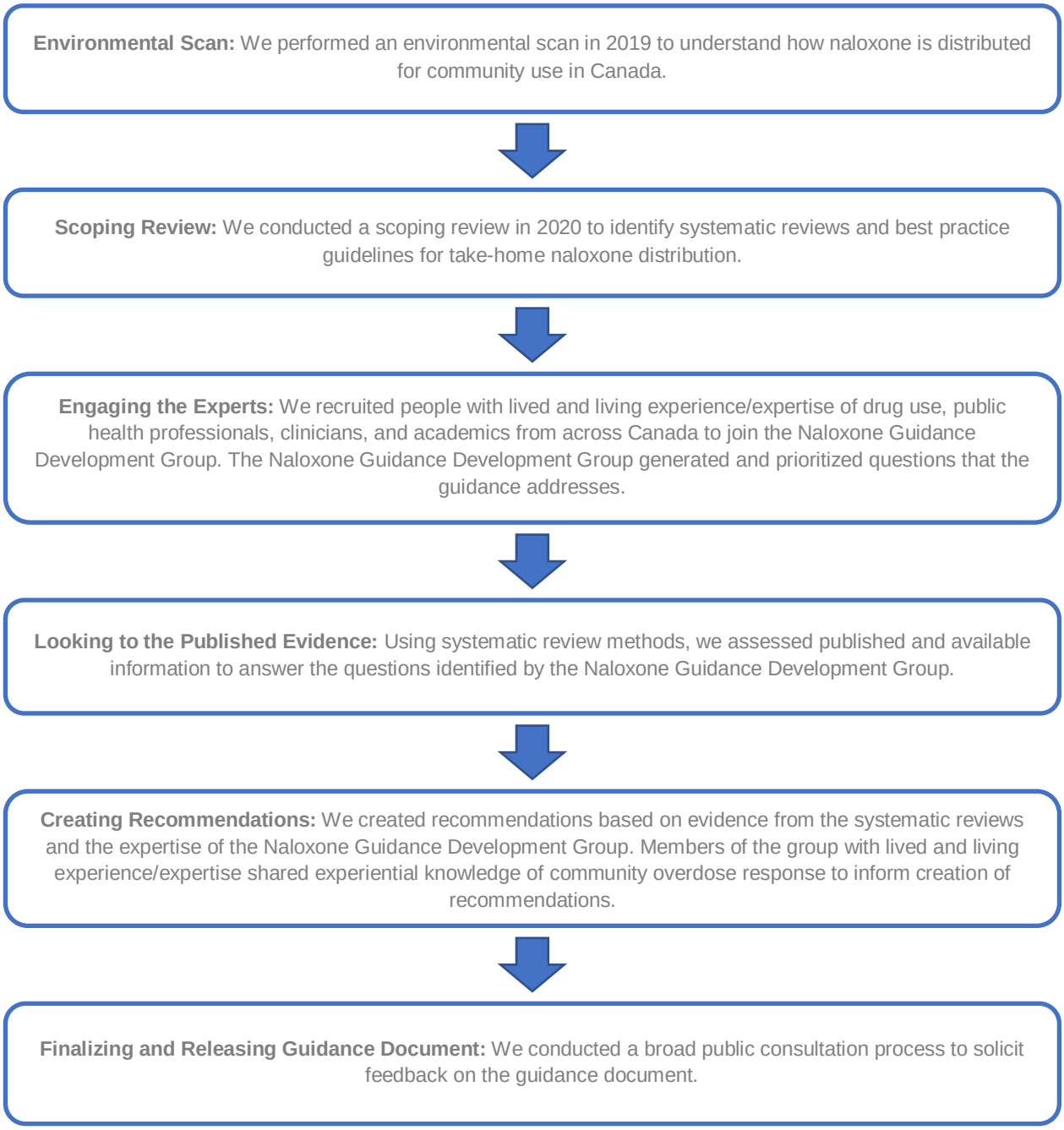

Figure 1: Project Overview

PRIOR PROJECT WORK

Members of the research team conducted an environmental scan of naloxone access and distribution in 2019 with the aim of mapping existing practices and identifying barriers to distribution across Canada (Moustaqim-Barrette et al., 2019). Please click here to read the full environmental scan.

We conducted an umbrella scoping review (a review of published reviews) to characterize the existing knowledge base related to the use of naloxone in the community setting and to identify gaps in the literature (Moustaqim-Barrette, Dhillon, et al., 2021). Please click here to read the full umbrella scoping review. A total of 47 reviews were identified on topics including naloxone dosing or routes of administration; provision, feasibility, and acceptability of naloxone distribution; effectiveness of naloxone for opioid overdose; overdose response after naloxone administration; naloxone training and education; recommendations for policy, practice, and gaps in knowledge; naloxone safety; and cost effectiveness.

ENGAGING THE EXPERTS

During guidance development, we engaged a variety of stakeholders to reflect the needs and values of those using the final guidance document and those using THN services. This included people who use drugs, those delivering services including people who use drugs, harm reduction and overdose response workers, public health professionals, clinicians, and program leaders. We also engaged academics with expertise in harm reduction to ensure we used a rigorous methodological approach.

RECRUITING THE NALOXONE GUIDANCE DEVELOPMENT GROUP

Public health guideline development projects benefit from diverse groups of stakeholders (Hilton Boon et al., 2021). Study principal investigators and Canadian Research Initiative in Substance Misuse (CRISM) partners nominated members to participate in the Naloxone Guidance Development Group. The Naloxone Guidance Development Group was composed of subcommittees that provided input on the guideline development process. Using the snowball method, the initial members of each subcommittee nominated additional members into the Naloxone Guidance Development Group to diversify recruitment and expand the group membership. Those with lived and living experience/expertise of substance use; Indigenous, Black, and racialized people; and Two-Spirit, lesbian, gay, bisexual, transgender, and queer

people were explicitly invited in recruitment material. We targeted territories and provinces that were not already represented in the Naloxone Guidance Development Group in later stages of recruitment.

The 52-member Naloxone Guidance Development Group consisted of people with lived and living experience of substance use, frontline harm reduction and overdose response workers, academics specializing in harm reduction, and clinicians and public health professionals. People with lived and living experience/expertise are especially important to the project as THN program end users and experts (Lei et al., 2022; World Health Organization et al., 2014).

The Naloxone Guidance Development Group consists of eight subcommittees (in order of chronological involvement). Members could take part in more than one committee. The committees are:

- Leadership Group (three members): Provided formal academic supervision of the project. Members included clinicians and academics with expertise in harm reduction.
- Research Team (six members): Provided leadership and/or support of research activities including project coordination, systematic review work, meeting facilitation, conflict of interest review, and manuscript and report drafting. Members had experience in public health, harm reduction, healthcare, library sciences, and legal studies.
- Guidance Steering Committee (eight members): Steered guidance discussions, encouraged productive debate, and provided oversight of the guidance development process and encouraged productive debate. Members included people with lived and living experience/expertise of drug use and responding to overdoses, frontline overdose response and harm reduction workers, public health professionals, clinicians, and academics with expertise in harm reduction.
- Methodology Advisory Committee (four members): Provided advice on guidance development methods from a health research perspective.
- Affected Community Committee (eight members): Provided direction and recommendations on the values and preferences of people with lived and living experience/expertise related to take-home naloxone distribution and use in opioid overdose. Members included frontline overdose response and harm reduction workers, public health professionals.
- Clinical Expert Committee (11 members): Provided direction and recommendations on the use of naloxone in opioid overdose from a clinical viewpoint. Professional groups represented included harm reduction workers, pharmacists, nurse practitioners, and physicians.
- Guidance Development Panel (14 members): Voted on key questions that the guidance addresses as part of a Delphi process. The Affected Community Committee, Guidance Steering Committee, and Clinical Expert Committee were all invited to join the Guidance Development Panel. Members included people with lived and living experience/expertise of drug use and

responding to overdose, frontline overdose response and harm reduction workers, public health professionals, clinicians, and academics with expertise in harm reduction.

- External Review Committee (eight members): Provided independent and objective assessments of the process and conclusions attained throughout the guidance development process. Members included people with lived and living experience/expertise of drug use and responding to overdoses, public health professionals, clinicians, and academics with expertise in harm reduction both from Canada and internationally.

The project was pan-Canadian in scope and the Naloxone Guidance Development Group met regularly through Zoom teleconferencing software. Individuals with lived and living experience/expertise participating in the Naloxone Guidance Development Group who were not compensated for this work through their workplace received $25/hour honoraria (Becu & Allan, 2018).

SELECTING QUESTIONS TO ADDRESS IN THE GUIDANCE

We engaged the Guideline Development Group in an adapted Delphi process to select questions that were most useful to address in the guidance development project (Black et al., 1999; McMillan et al., 2016). We conducted a scoping literature review to identify published systematic reviews on the topic of THN to understand the nature of the evidence and to generate a list of questions that a guidance could address (Moustaqim-Barrette, Dhillon, et al., 2021). The research team took this preliminary list of questions to the Guidance Steering Committee, Affected Community Committee, and Clinical Expert Committee. The committees assessed whether the questions were clear and provided further questions of interest. The Guidance Development Panel voted on proposed key questions using the Delphi process. The Delphi process is a consensus-building strategy that we used to identify what questions we should address in the guidance based on how important the Guidance Development Panel rated each question (Black et al., 1999; McMillan et al., 2016). Participants used REDCap software to rate proposed questions using a 5-point Likert scale (strongly agree/agree/neutral/disagree/strongly disagree where strongly agree = 1 and strongly disagree = 5) and free text comments were used to explain how they rated importance. After the first round of questionnaires was collated and the results presented back to the group, the Delphi process was repeated for a second round of input. Three research questions voted as most important in the first round of voting (and rated as important in the second round) were then used to develop systematic reviews to provide evidence to the guidance. For more details on the Delphi process please click here to read our publication (Ferguson et al., 2022).

LOOKING TO THE PUBLISHED EVIDENCE

We conducted three systematic reviews of the scientific and grey literature according to the GRADE framework to identify resources for guidance development beyond what was initially found in the scoping review (Zhang et al., 2019). We sought to answer three research questions identified as important by the Naloxone Guidance Development Group. More details on the systematic review methods can be found in Appendix 2 of the published manuscript (Ferguson et al., 2023). See the research questions in table 2.

Table 2: Research Questions Table

Topic	Research Question
Route of Administration	What is the effect of intramuscular vs intranasal naloxone administration in community setting on morbidity or mortality of persons experiencing opioid overdose?
Kit Contents	What is the evidence to support the impact of specific naloxone kit contents on outcomes including infection control, preference, or health outcomes? This question is framed from both the perspective of people experiencing overdose and people responding to overdose in the community setting.
Overdose Response	Are there different rates of mortality and morbidity for persons experiencing opioid overdose in community settings associated with various overdose responses in addition to naloxone administration: a) rescue breathing, b) conventional cardiopulmonary resuscitation (CPR) including rescue breathing, c) compression-only CPR, or d) neither rescue breathing or chest compressions?

Prior to completing the systematic reviews, we conducted a scoping review discussed above with the goal of identifying previously conducted systematic reviews (Moustaqim-Barrette, Dhillon, et al., 2021). None of the identified systematic reviews focused on community overdose response (rated high quality using the AMSTAR appraisal tool, Shea et al., 2017). There is more information on the research questions on route of administration, kit contents, and overdose response in their respective sections in the report.

INCLUSION CRITERIA

To get a broad understanding of our research questions we did not limit our literature searches by either date or study design. We included sources that were written in either French or English because they are the official languages of Canada and matched team linguistic capacity.

DATA SOURCES

We conducted searches on both academic and grey literature due to the nature of how public health evidence is disseminated (Hilton Boon et al., 2021). We searched the academic literature by looking at the following databases for relevant sources:

- MEDLINE
- EMBASE
- CINAHL
- PsycINFO
- Epistemonikos
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews

We searched the grey literature search by looking at the following:

- grey literature databases (including Guidelines International Network (GIN), Open Grey: System for Information on Grey Literature of Medicine, and Grey Literature Report),
- customized Google searches where the first 100 hits were evaluated,
- customized Google searches for existing public-facing guidelines on THN within Canada including territorial and provincial names as key words,
- targeted websites including government websites in Canada, United States, Europe, and Australia, reflecting regions affected by the overdose crisis related to regional drug supply, and non-governmental and think tank websites including the Bill and Melinda Gates Foundation, WHO, United Nations, Canadian Centre on Substance Use and Addiction (CCSA), and the Canadian Agency for Drugs and Technology in Health (CADTH)

We also solicited further research from content experts, performed citation chaining, and looked through funding databases from the Canadian Institutes of Health Research and the National Institutes of Health in the USA as well as PROSPERO (a database that registers protocols of systematic reviews, rapid reviews, and umbrella reviews). For the PRISMA diagrams summarizing how we identified published evidence, search dates, search strategies,

and quality of published academic and grey literature evidence please see Appendix 2 of the published manuscript (Ferguson et al., In Press).

IDENTIFYING RELEVANT SOURCES

Two members of the research team screened all articles identified in the search for relevance by title/abstract in duplicate. Full text screening for sources identified through title/abstract screening was also completed in duplicate. We used Covidence software to organize screening (Veritas Health Innovation, 2022). If team members disagreed about the relevance of an article, the team reached consensus through informal discussion.

DATA EXTRACTION

Two team members extracted data and performed quality assessment for all identified relevant sources in duplicate using REDCap software.

We chose to use the Public Health Ontario MetaQAT tool to critically appraise the literature identified through systematic reviews (Ontario Agency for Health Protection and Promotion (Public Health Ontario) et al., 2015). The MetaQAT was developed to accommodate the different kinds of study designs that public health research often relies on. The MetaQAT assesses relevancy, reliability, validity, and applicability.

We extracted data on article title, journal title (if applicable), date, authors, country where study was conducted, study design, study objective or research questions, study population, sample size, data source, analyses, main findings and conclusions, and effect measures.

CREATING RECOMMENDATIONS

We used the GRADE framework to determine the strength of recommendations (Schünemann et al., 2013). We assessed whether we could quantitatively combine findings and found that much of the research looked at different outcomes using study designs that were not appropriate for meta-analysis (Higgins & Cochrane Collaboration, 2020). We described the identified studies based on outcomes and relevance to guidance development (Campbell et al., 2020).

We used the GRADE framework in guideline development to ensure methodological rigour (Hilton Boon et al., 2021). We chose the GRADE tool because it is designed to grade quality of published academic and grey literature evidence and help develop recommendations

using systematic, transparent, and reproducible methods with the understanding that subjectivity exists in determining quality of published academic and grey literature evidence (Siemieniuk & Guyatt, 2019). The published academic and grey literature evidence that was identified through systematic reviews was graded based on GRADE criteria of risk of bias, imprecision, inconsistency, indirectness, and publication bias (Siemieniuk & Guyatt, 2019).

FINALIZING AND RELEASING THE GUIDANCE

A key element to developing guidelines in the public health field is to promote health equity (World Health Organization, 2014), and we aimed to center the health and wellbeing of people who use drugs in the guidance development project (Adams et al., 2022)

The leadership group and research team generated preliminary recommendations and strength of recommendations based on the published evidence from the systematic reviews. The proposed recommendations and strength of recommendations were sent to the Guidance Steering Committee, Affected Community Committee, and Clinical Expert Committee. We collected feedback on the content and wording of the recommendation, strength of recommendation, and components contributing to strength of recommendation (desirable versus undesirable consequences, strength of published academic and grey literature evidence, values and preferences of affected community, and resource use) via REDCap survey software. For details on the feedback surveys completed by the Guidance Steering Committee, Affected Community Committee, and Clinical Expert Committee, see Appendix 5 of the published manuscript (Ferguson et al., In Press).

Additionally, we used the feedback surveys to collect community evidence. In this guidance, we defined community evidence as knowledge from people with lived and living experience or expertise of drug use, overdose, and overdose response generated from observations and experiences (Schünemann et al., 2019). Expert evidence can be an effective way to develop robust and trustworthy guidelines in an absence of published evidence (Schünemann et al., 2019). This data source was especially important since the published evidence was of very low quality, sometimes regionally specific to locations outside of Canada, and sometimes varied on key issues. Subsequently, the leadership and research team, Methodology Advisory Committee, Guidance Steering Committee, Affected Community Committee, and Clinical Expert Committee met and reached informal consensus together on recommendations using Zoom teleconferencing software. See Figure 2 for an overview of community engagement.

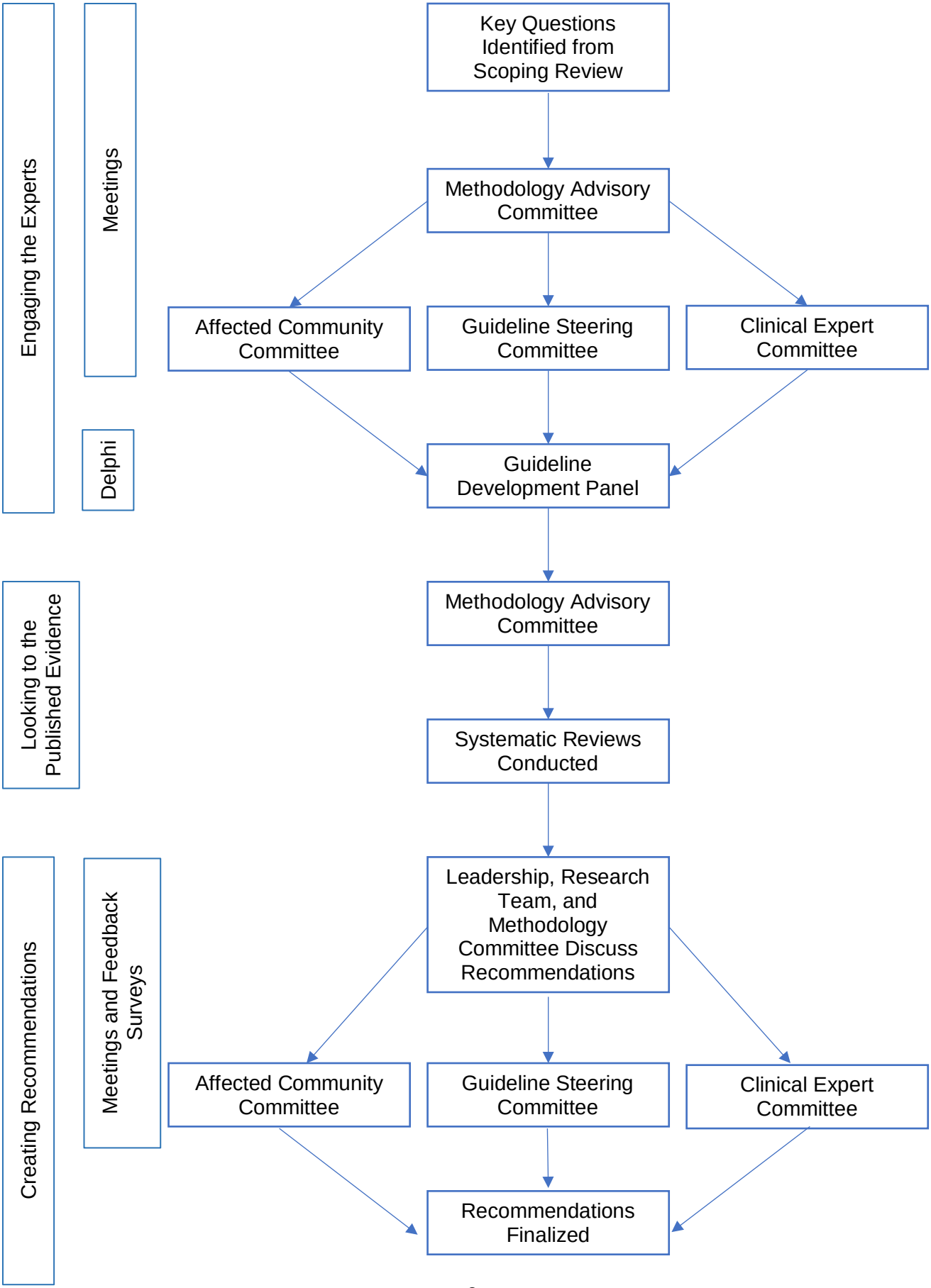

Figure 2. Overview of Community Engagement

We reviewed the key domains and checklist items of the AGREE II tool to ensure thorough reporting of guidance development methods (Brouwers et al., 2016). The AGREE II tool rates guidelines on each of the following criteria: scope and purpose, stakeholder involvement, rigour of development, clarity of presentation, applicability and editorial independence (Brouwers et al., 2016).

FEEDBACK ON THE GUIDANCE REPORT

The Guidance Steering Committee, Affected Community Committee, Clinical Expert, and Methodology Advisory Committee reviewed the final guidance report and gave content and style feedback. The External Review Committee then reviewed the guidance report.

The Canadian Take-Home Naloxone Program Guidance report was publicly available on the CRISM website for public input for six weeks alongside a survey to collect feedback. Those who completed the survey were entered into a draw for one of two $100 Visa gift card.

During the public input period, the research team also specifically sought out feedback from people with lived and living experience/expertise of substance use and those working on the frontlines of the overdose crisis not otherwise included in the project. We conducted virtual consultation meetings in which participants commented on finalized recommendations as well as facilitators and barriers to implementing recommendations. Each participant was financially compensated with $50 honorarium (Becu & Allan, 2018). See details of public input below.

RECOMMENDATIONS

STRENGTH OF RECOMMENDATION DEFINITION

The recommendations within this guidance report are most applicable to policy makers, funders, and organizations developing and managing THN programs. The GRADE framework defines strong and conditional policy recommendations as:

Strong Recommendation: The recommendation can be adapted as policy in most situations and/or regions (Schünemann et al., 2013).

Conditional Recommendation: Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions (Schünemann et al., 2013).

While the term “weak recommendation” is often used, conditional may be more appropriate in the public health context (Hilton Boon et al., 2021). The GRADE framework stresses the importance of separate judgements about the quality of the evidence and the strength of recommendations; while strong recommendations may be more judiciously issued in the context of low quality evidence they are in line with the framework (see section 1.2 in the GRADE handbook) (Schünemann et al., 2013).

ROUTE OF ADMINISTRATION

BACKGROUND

Naloxone can be administered by intramuscular (injection into muscle), subcutaneous (injection into the tissue between the skin and the muscle), intravenous (injection into a vein), or intranasal (sprayed into the nasal passages) routes (Dezfulian et al., 2021). THN is available in Canada through intramuscular or intranasal routes (Moustaqim-Barrette et al., 2019).

RESEARCH QUESTION

What is the effect of intramuscular vs intranasal naloxone administration in community setting on morbidity or mortality of persons experiencing opioid overdose?

PICO BREAKDOWN

We used the PICOS model (Population/Problem, Intervention/Exposure, Comparison, Outcome/Findings, Healthcare Setting/ Context) to describe our research question.

P: Adults and mature minors (13 years and over) experiencing overdose

I: Intranasal route of administration for naloxone

C: Intramuscular route of administration for naloxone or no comparison

O: Morbidity (including but not limited to anoxic brain injury, pulmonary edema, etc.) and mortality

S: In community setting outside of a professional role

SUMMARY OF PUBLISHED EVIDENCE

We identified ten sources that were relevant to our research question including: three narrative reviews (Lewis et al., 2017; Strang et al., 2019; Weaver et al., 2018), two systematic reviews (Chou et al., 2017; Mueller et al., 2015), grey literature including two rapid reviews and one health technology assessment (Health Technology Assessment Unit, 2020; Peprah & Frey, 2017; Peprah & Severn, 2019), one umbrella review of systematic reviews (Razaghizad et al., 2021), and one clinical guideline (World Health Organization et al., 2014). The studies' outcomes included effectiveness of overdose reversal, and overdose-related morbidity. Most studies included in this review drew conclusions about the comparative effectiveness of intranasal and intramuscular naloxone in reducing overdose-related morbidity and mortality. However, none of the studies identified any primary research that satisfied eligibility criteria for the present review. The body of evidence drew heavily on two randomized controlled trials conducted in Australia by Kelly et al. (2005) and Kerr et al. (2009). These studies, which enrolled a total of 327 patients, compared intranasal and intramuscular administration of naloxone by paramedics, rather than community members.

Seven studies reported on overdose reversal (Chou et al., 2017; Lewis et al., 2017; Mueller et al., 2015; Peprah & Frey, 2017; Razaghizad et al., 2021; Strang et al., 2019; Weaver et al., 2018). Four studies concluded that intranasal and intramuscular naloxone had similar efficacy (Chou et al., 2017; Lewis et al., 2017; Mueller et al., 2015; Strang et al., 2019), although Strang et al. noted that rescue naloxone (i.e. a second naloxone dose by injection) was more likely to be needed when naloxone was administered intranasally with an atomizer attached to a syringe. Weaver et al. (2018) recognized both routes of administration as potentially effective but suggested that intranasal atomizers were preferable "when considering cost, effectiveness,

and administrator safety" (p. 91). The studies that Weaver et al. base their conclusions on looked at 2 mg of naloxone administered using either intranasal or intramuscular routes compared to the higher dosages used in contemporary Canadian THN programs (4mg) (Kelly et al., 2005; Kerr et al., 2009). Using data from the same two studies, Peprah and Frey (2017), in contrast, found that intramuscular naloxone had "[at least] nominally higher efficacy" (e.g., achieved adequate response, faster time to adequate response, and fewer patients needing rescue naloxone.) (p. 14). Razaghizad et al. (2021) stated that high-concentration intranasal naloxone (> 2 mg/mL) was as effective as intramuscular naloxone, but that lower concentrations were less effective.

One guideline reported on overdose-related morbidity (World Health Organization et al., 2014). Morbidity outcomes included hospitalization following overdose reversal and adverse events. The WHO conducted a meta-analysis of two randomized controlled trials (Kelly et al., 2005; Kerr et al., 2009) and found no difference between intranasal and intramuscular naloxone for these outcomes.

RECOMMENDATION

Take-home naloxone programs should offer both intramuscular and intranasal formulations of naloxone, so that people accessing naloxone kits can choose their preferred formulation.

STRENGTH OF RECOMMENDATION

We categorized the recommendation on routes of administration as conditional because of the following factors:

Balance of desirable and undesirable consequences: Little evidence was available for comparison between routes of administration by community overdose responders.

Quality of published academic and grey literature evidence: The quality of published evidence for outcomes identified in the literature (overdose reversal and overdose-related mortality) was rated as very low, in part because it was not directly applicable to community overdose responders. For more details see Appendix 3 on systematic review findings in our published manuscript (Ferguson et al., In Press).

Values and preferences of those affected: Published literature supports the finding that many people who use drugs prefer intranasal naloxone because of ease of use and concerns over

needle stick injuries (Boeri & Lamonica, 2021; Neale et al., 2021). Members of the Naloxone Guidance Development Group reported that many people prefer intramuscular versus intranasal because it is perceived as more effective and because it is familiar for many community overdose responders. Other responders in the Naloxone Guidance Development Group report that among their fellow overdose responders, intranasal is preferred for ease of use but perceived as less reliable compared to intramuscular.

Resource use: A barrier to uptake of intranasal naloxone is higher cost (Moustaqim-Barrette et al., 2019; Peprah & Frey, 2017). Currently intranasal naloxone is only available in Canada through one manufacturer (Health Canada, 2016).

KEY CONSIDERATIONS

Ease of Use and Accessibility

The Naloxone Guidance Development Group discussed how ease of use is an important consideration for responders that may have physical coordination or mobility issues preventing them from preparing intramuscular naloxone. By providing more options, THN will be accessible for a range of people including those with disabilities.

Ease of Use and Other Considerations

Naloxone Guidance Development Group members discussed that ease of use is also important considering high-stress overdose situations. Groups of people who might be better served by intranasal versus intramuscular naloxone are those with barriers to using needles for a variety of reasons, such as needle aversion. Group members discussed how inexperienced individuals, such as some family members of those who use drugs, may prefer intranasal naloxone.

Differences in Pharmacokinetics

Intranasal naloxone absorption may vary compared to intramuscular naloxone; so someone might absorb a higher or lower dose of naloxone than intended (Dale, 2022). For example, intranasal naloxone absorption may differ when someone has septal abnormalities, nose bleeding, nasal mucous or trauma (Dale, 2022) or for people with scar tissue such as occurs with a history of cocaine use (Joint Task Force on Overdose Response, 2017). The Naloxone Guidance Development Group observed that while intranasal naloxone is extremely valuable for ease of use, members have noted that, in practice, it is more likely to precipitate

withdrawal. Naloxone Guidance Development Group members highlighted the importance of distribution programs clearly communicating the benefits and drawbacks of different routes of administration.

Some experienced community overdose responders report titrating, or slowly increasing, the amount of naloxone administered in order to prevent withdrawal. Titration is only possible in the community setting with intramuscular versus intranasal naloxone. Intranasal doses are determined by the pharmaceutical companies which make them (Dale, 2022).

New Dosages of Intranasal Naloxone

Dosage of intranasal naloxone varies internationally. For example, in the United Kingdom and Australia, Nyxoid is available in1.8 mg doses (Datapharm, 2021; MUNDIPHARMA, 2020). In the USA, the Food and Drug Administration approved a higher dose of intranasal naloxone of 8 mg in 2021, double the next highest available dose of 4 mg (the dosage available in Canada). Some advocates are concerned that the increased doses resulted in negative experiences of withdrawal and may contribute to reluctance to being administered the life-saving medication (Hill et al., 2022). Other people preferred to receive higher-dose nasal naloxone, especially those with recent suspected fentanyl exposure (Strickland et al., 2022).

Our recommendation is specific to the 4 mg dose available in Canada.

Some Naloxone Guidance Development Group members spoke against introducing the higher dosage in Canada as intranasal naloxone cannot be titrated, increasing the risk of precipitating withdrawal.

Gaps in Evidence

People administering naloxone in the community reported instances of intranasal not working, presumably because of trauma or scarring of the nasal passages or septum deviation. In a randomized control trial on the topic, people experiencing overdose who were administered intranasal naloxone were more likely to require an additional administration of naloxone compared to people who received intramuscular naloxone (Dietze et al., 2019). Current community knowledge suggests first administering intranasal naloxone, and if that is ineffective, to switch to intramuscular naloxone. The Naloxone Guidance Development Group identified the need for guidance on how long to wait before administering the intramuscular naloxone.

KIT CONTENTS

RESEARCH QUESTION

What is the evidence to support the impact of specific naloxone kit contents on outcomes including infection control, preference, or health outcomes? This question is framed from both the perspective of people experiencing overdose and people responding to overdose in the community setting.

PICO BREAKDOWN

We used the PICOS model (Population/Problem, Intervention/Exposure, Comparison, Outcome/Findings, Healthcare Setting/Context) to describe our research question.

P: Adults and mature minors (13 years and over) experiencing overdose in community setting or responding to overdose in community setting
I: Naloxone kit distribution at the community level
C: Kit contents or no comparison
O: Included but not limited to infection control, preference, or health outcomes (morbidity, mortality)
S: In community setting outside of a professional role

SUMMARY OF PUBLISHED EVIDENCE

The research question for the systematic review on kit contents was left intentionally broad to ensure a comprehensive review of the evidence on kit contents. We found 23 sources describing choice of kit contents, instructions for naloxone kit use, choice of naloxone delivery device, and inclusion of kit tracking technology. We did not locate sources directly comparing kit contents so are largely relying on descriptions of current practice to inform recommendation development.

Standard Kit Contents

Five documents from the grey literature discussed kit contents used in different jurisdictions (Alberta Health Services Harm Reduction Services, 2020b, 2020a; Canadian Mental Health Association Ontario, 2018; College of Pharmacists of Manitoba, 2020; Moustaqim-Barrette et al., 2019). Injectable naloxone kits generally contained:

- either two or three 0.4mg/ ml ampoules or vials of injectable naloxone;
- materials to support injection such as syringes and alcohol swabs for cleaning the injection site;
- personal protective equipment (PPE) including disposable gloves, breathing mask, and in some cases an ampoule breaker;
- instructions for naloxone use;
- and a carrying case.

Nasal naloxone kits generally contained (Alberta Health Services Harm Reduction Services, 2020a; Canadian Mental Health Association Ontario, 2018; College of Pharmacists of Manitoba, 2020; Moustaqim-Barrette et al., 2019):

- two 4mg/0.1ml nasal spray devices;
- PPE, including a breathing mask and disposable gloves;
- instructions for use;
- and a carrying case.

Moustaqim-Barrette et al. (2019) reported that provinces and territories in Canada differ in the number of ampoules or vials included in kits and whether intranasal kits are publicly funded and distributed. Across Canada intranasal naloxone kits are available to: clients of Veterans Affairs Canada; First Nations individuals with a valid status card and personal health number through the Non-Insured Health Benefits program (for First Nations individuals in all provinces and territories other than British Columbia); and through the First Nations Health Benefits Program for First Nations people in British Columbia. Moustaqim-Barrette et al. (2019) report that some provinces and territories added a third vial or ampoule in naloxone kits due to preliminary literature and surveillance demonstrating that some individuals required a higher number of doses of naloxone to reverse overdose as potent opioids emerged in the illegal supply.

The Institut National d'Excellence en Santé et en Services Sociaux (INESSS) recommends that naloxone kits use distinctive carrying cases that can easily be recognized during an overdose emergency (Jobin & Rossignol, 2018). INESSS also recommends that kits contain a rescue breathing mask so that those witnessing overdoses can respond to the best of their ability (Jobin & Rossignol, 2018). This is consistent with WHO guidance on overdose response, which states that CPR mouth barriers should be used for rescue ventilation when available (World Health Organization et al., 2014).

Instructions for Naloxone Kit Use

Six documents discussed user comprehension of instructions included in naloxone kits, including three mixed methods studies (Cohen et al., 2020; Harvey & Bubric, 2020; Rowe et al., 2020) and three documents from the grey literature (Gottlieb, 2019; Harvey, 2020; VandenBerg et al., 2019).

Cohen et al. (2020) conducted a study investigating levels of comprehension of the U.S. Food and Drug Administration's model "drug facts label" for over-the-counter naloxone. In a mixed methods study, Harvey & Bubric (2020) found that calling 911 was missed in 44% of simulated scenarios using the instruction sheets in the first phase of their research although it should be noted that some may not phone emergency medical services due to concerns about criminalization. Harvey & Bubric (2020) engaged in co-design with experienced and inexperienced naloxone administrators to improve instructions that were frequently overlooked. They found that participants may be reluctant to administer naloxone without information on the consequences of administration and that graphic information was particularly important. Other knowledge translation products from the same research program state that manufacturer labeling regulations can compromise legibility and readability, and emphasize the importance of collaborating with end-users with differing degrees of experience (Harvey et al., 2021; Rowe et al., 2020; VandenBerg et al., 2019). Harvey (2020) shared these findings on a website asserting the value of co-design.

Choice of Naloxone Delivery Device

Five sources discussed choice of naloxone delivery device (or the tool or technology used to deliver naloxone) including: one narrative review (Strang et al., 2019), one conference abstract (Orkin et al., 2015), one randomized control trial (Eggleston et al., 2020), one qualitative study (Neale et al., 2021), one mixed methods study (Lintzeris et al., 2020), and one qualitative study (Tippey et al., 2019)..

Alternate delivery devices such as pre-filled syringes and auto-injectors have higher costs, but there is evidence that they have high usability and are well-received by people who use drugs (Lintzeris et al., 2020; Neale et al., 2021; Strang et al., 2019; Tippey et al., 2019). We have elected not to include alternate delivery devices in recommended kit contents because of their current lack of availability in Canada.

Inclusion of Kit Tracking Technology

A program of research investigated the feasibility and acceptability of integrating low-energy Bluetooth real-time location systems into naloxone kits (J. T. Lai et al., 2017a, 2017b, 2018, 2020). This technology was designed to improve understanding of naloxone distribution patterns and populations of people who use drugs and might be reluctant to engage with the medical system.

Some participants communicated fears about active tracking technologies although study personnel stated that tracking would be passive[1]. THN kits were perceived as so important that access to kits overcame tracking as a barrier for service users (J. T. Lai et al., 2020), which may reflect the high importance placed on this life-saving intervention. As this intervention is resource-intensive and the study population voiced concerns about its use, we do not recommend it.

RECOMMENDATION

All take-home naloxone kits should include:

- A recognizable carrying case
- Non-latex gloves
- A rescue breathing mask
- Instructions on naloxone administration.
    - Instructions on how to administer naloxone should be designed in collaboration with people who use these kits. Take-home naloxone programs can use previously developed instructions or develop their own in collaboration with the affected community.

Intramuscular take-home naloxone kits should include:

- Three or more 0.4 mg/ml naloxone ampoules or vials based on program discretion and local experience (more ampoules or vials may be necessary in communities with high prevalence of illicitly manufactured fentanyl and other potent synthetic opioids)
- A syringe and needle for each ampoule or vial of naloxone
- Alcohol swabs
- Ampoule breaker (in kits containing ampoules)

[1] Authors describe a real-time location system that utilizes radiofrequency identification used to determine whether a naloxone kit had been taken off a hospital campus.

Intranasal take-home naloxone kits should include:

- Two 4 mg/0.1ml intranasal devices

STRENGTH OF RECOMMENDATION

We categorized the recommendation on naloxone kit contents as strong because of the following factors:

Balance of desirable and undesirable consequences:

- Inclusion of three ampoules rather than two may increase the rate of successful overdose reversal. Published evidence suggests that additional doses of naloxone may be necessary in overdoses involving fentanyl and other potent opioids (Karamouzian et al., 2019; Moe et al., 2020). There is also evidence suggesting that higher doses are associated with increased risk of moderate or severe withdrawal symptoms (Moustaqim-Barrette, Papamihali, et al., 2021). This risk may be offset by providing additional training in dose titration.
- Rescue breathing masks and other forms of personal protective equipment may reduce the risk of infection transmission, although the risk of COVID-19 transmission during overdose response remains ill-defined (Fragkou et al., 2021). PPE may also increase layperson willingness to administer naloxone and provide rescue breaths (Dezfulian et al., 2021).
- Instructions for naloxone use may be improved by including community members in design and usability testing, potentially increasing the probability of successful administration (Harvey & Bubric, 2020). This approach may increase development costs.

Quality of published academic and grey literature evidence: The overall quality of published evidence across all critical outcomes was ‘very low’. For more details, See Appendix 3 in our published manuscript (Ferguson et al., In Press).**Values and preferences of those affected:** There is evidence to suggest that community overdose responders prefer to use a barrier device when providing rescue breathing (Dezfulian et al., 2021).

Resource use: A systematic review of economic evaluations of THN programs in a variety of settings found that evaluations were consistent in finding the programs cost-effective, suggesting that the number of naloxone ampoules and other minor variations in kit contents (such as the type of carrying cases, syringes, or personal protective equipment) are unlikely to impact overall cost-effectiveness (Cherrier et al., 2022).

KEY CONSIDERATIONS

Number of Vials or Ampoules of Naloxone

The Naloxone Guidance Development Group reported that, in practice, a wide range of vials and ampoules are distributed by THN programs from two up to ten at a time (as determined by front line workers). Many group members advocated for more vials or ampoules of naloxone, so responders have sufficient naloxone available to save a life. This key consideration outweighs the risk of unused vials or ampoules or the risk of responders administering too much naloxone since responders can be trained to mitigate severe withdrawal. Additionally, respondents reported that people in rural or remote regions may wish to have more vials or ampoules available since distribution sites might be far away. Group members reported people getting multiple kits at a time to ensure they had sufficient naloxone and theorized that might be more expensive for distribution programs relative to including more naloxone per kit. Naloxone Guidance Development Group members did not suggest adding more intranasal naloxone doses, since lack of response may indicate issues of absorption through the nasal route, and the responder may want to switch to using intramuscular naloxone.

Some committee members would prefer more than three vials/ampoules but feasibility issues such as lack of ability to fit more vials/ampoules into the currently used kits was raised by other members.

COVID-19 Considerations

While our recommendation on kit contents includes a rescue breathing mask, we did not find evidence on how much protection masks offer against COVID-19 transmission.

Additional Information

The Naloxone Guidance Development Group identified other information important to include in a THN kit including the naloxone's expiry date (on the outside of the case) and recommendations on protecting kit contents from temperature fluctuations (D. Lai et al., 2019).

The Naloxone Guidance Development Group also identified a need to include information on accessing resources on a variety of topics including locations and times of supervised consumption sites, where to access aftercare, or what to expect when someone is in withdrawal.

Recognisability of Kits

While the recognisability of kits appeared in guidance to help people respond quickly in times of crisis, Naloxone Guidance Development Group members also talked about the stigmatizing nature of being seen with THN kits. Some reported that people who use drugs had had their kits apprehended by police in the early days of naloxone distribution. Similarly, a report on the first phase of THN in Toronto, Ontario, also reported an incidence of kit apprehension by police (Leece et al., 2013)

Some of the Naloxone Guidance Development Group members reported that people often reuse carrying cases for other purposes after using naloxone, compromising the ability of responders to administer naloxone during an overdose.

Other Considerations

The Naloxone Guidance Development Group also reported that having a carabiner on THN kits makes them easier to carry. Safety syringes in THN may decrease risk of needlestick injury.

Gaps in Evidence

While outside of project scope, we identified the need for standardized strategies to monitor and change numbers of vials/ampoules in response to the illegal drug supply. Partners from Alberta reported that the number of vials/ampoules included in kits was increased from two to three based on dosage needed to revive data from Emergency Health Services. In British Columbia, the decision to increase the number of ampoules in 2016 was based on consultation with key stakeholders and on surveys returned by those who had administered naloxone (Towards the Heart: BCCDC Harm Reduction Services, 2019). Members of the Naloxone Guidance Development Group reported providing multiple kits to the same person so that they would be appropriately equipped to respond to overdose. We suggest the development of a standardized way to evaluate and potentially increase the number of vials/ampoules in Canada in collaboration with people with lived and living experience/expertise to reflect doses needed to reverse overdose in a specific region.

OVERDOSE RESPONSE

BACKGROUND

Community overdose response recommendations differ across Canada (BC Centre for Disease Control, 2022; City of Toronto, No Date; Mitra et al., 2016). Our goal was to review the literature, consult with the Naloxone Guidance Development Group, and then collaboratively generate guidance to help standardize practice.

PATHOPHYSIOLOGY

***Content warning**: This section discusses the physiological reasons why people die from opioid overdose. We encourage readers to pause and reach out to supports as needed.*

Overdose response must take the pathophysiology of opioid overdose into account. When someone experiences opioid overdose, their body's regulation of their breathing is impaired and respiration is depressed (their breathing slows and then stops) (Dezfulian et al., 2021). Since the person experiencing overdose is not breathing effectively, oxygen cannot reach the heart and the individual may experience cardiac arrest (their heart stops beating or beats too ineffectively to support their vital organs) (Dezfulian et al., 2021).

RESEARCH QUESTION

Are there different rates of mortality and morbidity for persons experiencing opioid overdose in community settings associated with various overdose responses in addition to naloxone administration: a) rescue breathing, b) conventional cardiopulmonary resuscitation (CPR) including rescue breathing, c) compression-only CPR, or d) neither rescue breathing nor chest compressions?

PICO BREAKDOWN

We used the PICO model (Population/Problem, Intervention/Exposure, Comparison, Outcome/Findings, Healthcare Setting/Context) to describe our research question.

P: Adults, and mature minors (13 years and over) experiencing suspected opioid overdose
I: Overdose response and naloxone administration including rescue breathing, chest compressions, or both rescue breathing and chest compressions administered by community overdose responders
C: Naloxone administration alone (i.e., neither chest compressions or rescue breathing) or no comparison
O: Mortality or morbidity (e.g., anoxic brain damage or pulmonary edema)
S: In community setting outside of a professional role

SUMMARY OF PUBLISHED EVIDENCE

A total of seven sources met criteria for our systematic review on overdose response including three guidelines (Dezfulian et al., 2021; Jobin & Rossignol, 2018; World Health Organization et al., 2014), a feasibility study (Seal et al., 2005), an evidence brief and three grey literature sources (Mitra et al., 2016; New York State, 2016; Ontario Agency for Health Protection and Promotion (Public Health Ontario) & Leece, 2016). See Appendix 2 in our published manuscript (Ferguson et al., In Press) for a PRISMA diagram, which breaks down how we identified these sources. Since there were no high-quality primary sources specific to our research questions to guide recommendations, guidance documents inform the published evidence discussed below.

Extant literature states that calling emergency medical services and administering naloxone are high priorities in the event of opioid overdose (Dezfulian et al., 2021; Jobin & Rossignol, 2018; Mitra et al., 2016; New York State, 2016; World Health Organization et al., 2014). Verbal and physical stimulation, especially painful stimulation, were noted to stimulate breathing and be important steps in overdose response (Jobin & Rossignol, 2018; New York State, 2016; World Health Organization et al., 2014). Members of the Naloxone Guidance Development Group with experience of naloxone administration supported the finding on the importance of administering stimuli.

GUIDANCE FOR TRAINED RESPONDERS

Training on Overdose Response

Guidance on overdose response often depends on the level of responder training. Training is important to improve knowledge and competency in responding to overdose, and empowers those encountering overdoses to respond (Jobin & Rossignol, 2018). The literature describes training received through overdose education and naloxone distribution programs, CPR training, and unspecified training.

Two sources discussed training that occurs specifically within Opioid Overdose Education & Naloxone Distribution programs (Dezfulian et al., 2021; Seal et al., 2005). The American Heart Association stated in a scientific statement that training may occur at Opioid Overdose Education & Naloxone Distribution programs although THN distribution programs should carefully consider whether they are positioned to provide sufficient training (Dezfulian et al., 2021).

Some sources discuss overdose response for responders specifically trained in CPR (Jobin & Rossignol, 2018; Mitra et al., 2016; Ontario Agency for Health Protection and Promotion (Public Health Ontario) & Leece, 2016). Jobin & Rossignol (2018) recommend conventional CPR (rescue breathing and compressions) with CPR training while Mitra, Schoffel, & Globerman (2016) recommend rescue breathing alone with CPR training.

The World Health Organization (2014) stated that training is necessary but did not specify where or how people should receive training. The Technical Working Group on Resuscitation Training in Naloxone Programs (New York State, 2016) states that programs should train participants in whatever kind of resuscitation technique the program decides is appropriate. Naloxone Guidance Development Group members emphasized the different ways that people learn from one another and from alternate sources such as online resources.

Decisions to recommend compression-only CPR have been based on the assumption that community overdose responders without basic life support training are unable to reliably recognize cardiac arrest and so should be considered “untrained” (Mitra et al., 2016; Ontario Agency for Health Protection and Promotion (Public Health Ontario) & Leece, 2016). On the other hand, individuals in the Naloxone Guidance Development Group with experience in responding to overdose and training others on overdose response reported widespread ability to recognize and react to either respiratory depression or cardiac arrest after training.

Within this guidance document, we consider training by another community overdose responder, online education, overdose education and naloxone distribution service, or CPR training as potential training strategies. It is outside of the scope of this project to determine *how* programs should conduct training.

Guidance for Trained Responders

Evidence on Overdose Response for Respiratory Depression

Guidance for ***trained*** responders from the Ontario HIV Treatment Network (Mitra et al., 2016) and the World Health Organization (2014) recommends providing rescue breathing only in the event of respiratory depression. The American Heart Association (Dezfulian et al., 2021) recommends providing conventional CPR including compressions and rescue breathing for trained lay responders when a person with suspected opioid poisoning is not breathing normally. We did not identify evidence in the scientific literature suggesting that either rescue breathing or conventional CPR is better in instances where someone is experiencing respiratory depression (without cardiac arrest) associated with opioid overdose.

A feasibility study from San Francisco, USA included information on survival following CPR and rescue breathing only; fortunately, all those experiencing overdose lived and as a result comparisons between the two responses were not possible (Seal et al., 2005).

Initially, based on the lack of published evidence and consensus, we considered including a recommendation for rescue breathing *or* conventional CPR (with both rescue breathing and compression) in addition to naloxone administration or not making a recommendation. The Naloxone Guidance Development Group did not endorse that approach, because an ambiguous recommendation or no recommendation could inadvertently lead to inaction when action would be a better course.

Evidence from the Naloxone Guidance Development Group

The Naloxone Guidance Development Group voiced strong support for rescue breathing only in the case of respiratory depression versus conventional CPR, which includes rescue breathing and chest compressions.

Pathophysiology

A key reason that the Naloxone Guidance Development Group prioritized rescue breathing over conventional CPR was the pathophysiology of opioid overdose. *As opioid overdose causes respiratory depression (slow or absent breathing) which leads to low levels of*

oxygen in the body (hypoxemia) which in turn causes cardiac arrest (when the heart stops or beats too ineffectively to support vital organs), group members felt that it was important to recommend the most physiologically appropriate response. Providing rescue breathing provides oxygen to the body, protecting the heart, brain, and other important organs (Mitra et al., 2016). Some members of the Naloxone Guidance Development Group reported having over two decades of experience responding to overdose with rescue breathing with positive results.

Harms Associated with Compressions

Another reason that the Naloxone Guidance Development Group moved to prioritize rescue breathing over conventional CPR is the harms associated with chest compressions if compressions are not physiologically needed when a person's heart is beating. Chest compressions are associated with significant trauma to the chest (Hoke & Chamberlain, 2004). An estimated 13-97% of people experience rib fractures during conventional CPR and 1-43% of people experience sternal fractures (Hoke & Chamberlain, 2004). Additionally, chest compressions are difficult to execute if someone has a disability or is intoxicated. Naloxone Guidance Development Group members described stigma against people who use drugs as a barrier to receiving pain management in hospital after incurring injuries because of compressions. Stigma from health professionals has been previously identified as a barrier to pain management among people who use drugs (Voon et al., 2018).

Evidence on Overdose Response for Cardiac Arrest

Guidance for ***trained*** responders from the American Heart Association (Dezfulian et al., 2021), Ontario HIV Treatment Network (Mitra et al., 2016) and the World Health Organization (2014) recommends providing conventional CPR including both rescue breathing and chest compressions in the context of cardiac arrest. Leece (2016) concluded bystander CPR for adults is likely to result in better outcomes if overdose response includes chest compressions in the context of cardiac arrest.

Much of the research on CPR studied people who experienced sudden cardiac arrest related to a cardiac illness (Dezfulian et al., 2021). In these instances, the heart stops before breathing does, so compression-only CPR can circulate a larger amount of remaining oxygen in the body relative to those who experience cardiac arrest secondary to respiratory depression (Dezfulian et al., 2021). In an opioid overdose, respiratory depression usually comes before cardiac arrest, so there is less oxygen remaining in the body and conventional CPR including

compressions and rescue breathing is understood to be more effective based on the pathophysiology of overdose (Dezfulian et al., 2021).

While a scientific statement released from the American Heart Association discusses the theoretical harm of administering naloxone during cardiac arrest and increasing cerebral metabolic demand, this concern was not mentioned elsewhere (Dezfulian et al., 2021). Based on the lack of published academic and grey literature evidence and strong support from Naloxone Guidance Development Group for naloxone, we recommend including naloxone in overdose response.

Guidance for Untrained Responders

THN programs provide training on opioid overdose response, so while this body of evidence was not considered sufficiently relevant for inclusion in the overdose response recommendation; we include a summary of findings below. Guidance for ***untrained*** responders is to perform compressions-only CPR (Dezfulian et al., 2021; Jobin & Rossignol, 2018; Ontario Agency for Health Protection and Promotion (Public Health Ontario) & Leece, 2016). Sources discussed how compressions-only CPR is simple to teach, an important consideration for recommendations for the general public (Jobin & Rossignol, 2018). Research on people experiencing out of hospital *cardiac arrest* (a potential outcome of some opioid overdose) showed no benefit to rescue breathing alone (Ontario Agency for Health Protection and Promotion (Public Health Ontario) & Leece, 2016). Ineffective rescue breathing may detract from other essential interventions and reduce effectiveness of overall resuscitation for responders unable to distinguish between cardiac arrest and respiratory depression (Dezfulian et al., 2021). While compression-only CPR may cause trauma to the person experiencing overdose, including broken ribs and sternum (Hoke & Chamberlain, 2004; Jobin & Rossignol, 2018) and decreasing levels of oxygen in the body will render it less effective as time passes (Panchal et al., 2020) it will circulate oxygen remaining in the body to the vital organs (Dezfulian et al., 2021). A key consideration for untrained responders is that any CPR is better than no CPR, and it will provide benefit over no intervention (World Health Organization et al., 2014).

RECOMMENDATION

Response to suspected opioid overdose should depend on the skill and comfort level of the responder. People accessing services at THN distribution sites may be trained on overdose

response through their peers, using online resources, a cardiopulmonary resuscitation (CPR) training course, or training developed by THN programs.

Trained community responders should follow these steps:

- Apply vigorous verbal and physical stimuli
- Call emergency medical services (EMS)[1]
- Administer naloxone[2]
- If the individual experiencing overdose is in respiratory depression, provide rescue breathing
- If the individual experiencing overdose is in cardiac arrest, provide conventional cardiopulmonary resuscitation (CPR) including rescue breathing and chest compressions

THN distribution sites without capacity to offer overdose response education should direct people to services that offer training, if needed.

[1] We acknowledge that many people who use drugs do not feel safe calling EMS, especially in jurisdictions where police commonly attend EMS calls for overdose.

[2] There is differing guidance on the order of naloxone administration and resuscitation. Our recommendation does not address order of response interventions.

STRENGTH OF RECOMMENDATION

We categorized the recommendation on overdose response as strong because of the following factors:

Balance of desirable and undesirable consequences: The most important consideration in overdose response is the preservation of life. Chest compressions are associated with broken ribs and sternum (Hoke & Chamberlain, 2004) and should be reserved for cardiac arrest, or when the responder is unable to perform other interventions.

Quality of published academic and grey literature evidence: The quality of published evidence is very low. For more details, see Appendix 3 in our published manuscript (Ferguson et al., In Press).

Values and preferences of those affected: Members of the Naloxone Guidance Development Group spoke strongly in favour of rescue breathing for someone experiencing respiratory depression related to opioid overdose.

Resource use: Different methods of overdose response do not appear to have significant resource implications (World Health Organization et al., 2014).

KEY CONSIDERATIONS

COVID-19 Transmission

The Naloxone Guidance Development Group relayed community knowledge of addressing potential COVID-19 transmission. One member reported a strategy where, when possible, the person providing rescue breathing should be chosen based on being a close contact with the individual experiencing overdose (or someone that the person overdosing already lives with or spends considerable time with) (BC Emergency Management, No Date). Other layers of protection include COVID-19 vaccination.

Atypical Overdoses

Education on recognizing respiratory depression is especially important considering the high levels of benzodiazepines currently adulterating the illegal opioid supply, where someone experiencing overdose may still be sedated after naloxone although their breathing may be restored (Purssell et al., 2021). Additionally, opioids and benzodiazepines may be in drugs sold as non-opioids such as stimulants. In these instances, recognition of respiratory depression is important versus relying on level of consciousness to determine if someone needs resuscitation.

Research Gaps

There is inconclusive and contradictory evidence about overdose response in the scientific literature and public health practice, specifically regarding overdose response in the event of respiratory depression. Further research on the subject led by people with lived and living experience/expertise would be beneficial.

It was out of the scope of this project to look at the order in which overdose response occurs, varying overdose response in the event of multiple responders attending an overdose, or multiple overdoses occurring at the same time. There are differences across Canada in the recommended order of response and research clarifying these steps would be valuable.

Some resources communicate respiratory depression and cardiac arrest using terms like “absence of regular breathing” and “no signs of life” (World Health Organization et al., 2014) or “not breathing normally” and “doesn’t have a pulse” (Dezfulian et al., 2021). We decided to use the terms “respiratory depression” and “cardiac arrest” due to their precision, but it was not

within project scope to understand how best to communicate these concepts. Some Naloxone Guidance Development Group members voiced the opinion that the differences in response across the country are confusing. In addition to consistency of response, it may be helpful to create guidance to help standardize how concepts are taught.

Dezfulian et al (2021) discussed the importance of hands-on training in overdose response as part of the American Heart Association scientific statement, while some Naloxone Guidance Development Group members talked about how community overdose responders learn in a variety of ways including from peers and from online sources. In a Canadian environmental scan, key informants from naloxone programs reported that training can last between ten minutes to one hour in most provinces and territories (Moustaqim-Barrette et al., 2019). A best practice document published in 2022 discussed the importance of needs-based training that might take as little as five minutes and reflects the training needs of the community responder (Wenger et al., 2022).

Naloxone Guidance Development Group members identified the recovery position as an important step in overdose response in later stages of the project. Discussion of when and how the recovery position should be used is an important topic for future discussion.

This guidance focuses on response to opioid overdose; however, overdose response in the context of opioid contamination with stimulants or stimulant consumption alone is a gap in the research and guidance.

Other identified knowledge gaps include how to respond when the person with respiratory depression or cardiac arrest is pregnant.

PUBLIC INPUT

PROCESS

Following guidance development, we asked for public input on the finalized report and our recommendations. A total of 73 people from across the country completed surveys online between August 1st and September 30th, 2022. Those who completed the survey were eligible to enter a draw for two $100 Visa cards. We also invited people who use or have used drugs and/or who respond to overdose in the community setting to participate in 90-minute consultation sessions where we presented our recommendations. Consultation session participants were compensated for their time with $50 honoraria. A total of 75 people participated in 15 consultation sessions.

INSIGHTS

We received strongly positive feedback on our preliminary recommendations and valuable context for take-home naloxone distribution in Canada. We also captured a couple themes on topics outside the scope of our recommendations that we present below. We used public input to help clarify wording and add context to our report.

INSIGHTS ON ROUTES OF ADMINISTRATION

There was strong support for this recommendation in public input. Most people that we spoke to who regularly respond to overdoses use and prefer intramuscular naloxone due to the ability to titrate so as not to precipitate withdrawal symptoms. However, most participants in the public input process were strongly supportive of increasing availability of intranasal naloxone. Additional reasons why public input participants support increased intranasal naloxone availability not mentioned above include:

- Speed of administration: An important consideration when the person experiencing overdose has muscle rigidity and the responder is unable to administer rescue breathing.
- Accessibility: Consultation session participants report that many people who use drugs and are living in poverty are missing digits or hands due to infection secondary to contamination of drug supply or frostbite. Consultation session participants reported facing physical accessibility barriers when trying to administer intramuscular naloxone.
- Ease of use: Ease of use was identified as particularly important in difficult administration conditions such as when a responder is experiencing extreme stress or administering

naloxone in the dark. While most consultation session participants reported preferring intramuscular naloxone, it was frequently mentioned that people who do not use drugs may not feel comfortable using intramuscular naloxone. Consultation session participants noted that while they would prefer to receive titrated intramuscular naloxone, it was important to ensure that family and friends who do not use drugs still feel comfortable administering naloxone.

- Considerations about the physical environment: In areas with extremely low temperatures, such as Northern Canada, needles may not be able to penetrate through layers of clothing and it may be difficult or unsafe to remove layers. Consultation session participants reported that their hands become numb in the cold making intramuscular administration difficult.
- Safety considerations: Consultation session participants reported being cut by broken vials or ampoules during overdose response.

INSIGHTS ON KIT CONTENTS

Consultation session participants supported this recommendation. Further suggestions included providing multiple pairs of gloves to offset glove damage or ensure sufficient supply if multiple responders were present to provide needed support, in addition to sturdier breathing masks.

Participants also identified the need for education when THN programs change kit contents.

INSIGHTS ON OVERDOSE RESPONSE

Individuals participating in public input largely supported our recommendation, but there was some disagreement. Two participants out of 148 did not feel that community overdose responders could be trained to check a pulse or provide rescue breathing. However, most participants reported providing rescue breathing in the event of an overdose and being comfortable determining if a person experiencing overdose is in cardiac arrest. Some stated that they had not been trained to provide rescue breathing. Participants reported broken ribs caused by chest compressions, identified as an undesirable outcome of intervention.

Consultation session participants report the need for increased focus on oxygenation over naloxone to avoid withdrawal symptoms while ensuring that those experiencing overdose are receiving sufficient oxygen. Participants reported that this approach maintains relationships with people who use drugs and ensures they are comfortable returning to services following an overdose. Many participants stated that they wanted additional training in overdose response and naloxone titration.

Another concern frequently raised in public input sessions was excessive force used when applying stimuli to try to rouse a person experiencing overdose. Excessive force can result in unnecessary bruising and pain. Additionally, sternal rubs are perceived as invasive by many people with breasts.

OTHER INSIGHTS

Some participants reported that they did not have regular access to THN. Participants from some jurisdictions report long periods of time where naloxone is not available on a near annual basis. Others report that staff in social service organizations such as shelters throw away naloxone kits due to anti-drug use stigma. People in some rural communities report experiencing stigma when requesting, carrying, or discussing naloxone.

While our recommendations did not address training, those who participated in the public input consultation sessions reported that it was an important topic to consider. Participants reported that the following points are important considerations when developing training for THN programs:

- People who use drugs need to be included in the development of training
- Training should be standardized across the country so that there are not significant differences in overdose response depending on where you are
- Indigenous communities should be included in the development of training
- Overdose response should be taught in a way that doesn't exclude those with darker skin tones (for example: teaching that lips turn blue in an overdose prevents responders from assessing the health status of people with darker skin)
- Training should emphasize issues of consent. There were reports of people administering naloxone to those who were verbally declining suggesting both issues with respect of bodily autonomy as well as an understanding of when naloxone is needed

- Training should take into account the knowledge and skillset of the individual. Obligatory minimum length of training is a barrier to participation of experienced responders
- More education on how to prevent precipitating overdose should be offered
- More training should be offered on aftercare both for the person experiencing overdose and for the responder. People experiencing overdose need kind and calm support
- Training should occur using the equipment that will be available in the field (specifically breathing masks)
- Separate training should be provided for basic and advanced overdose response. Basic training can focus on speed while advanced training can incorporate concepts like naloxone titration
- People should be financially compensated for participating in training. They act as first responders and training interferes with their ability to earn money through other avenues
- Youth should be engaged in naloxone education

DISCUSSION

Guidance development in public health faces unique challenges as the health effects of interventions for large populations are more complicated to measure compared to interventions for individuals (Siemieniuk & Guyatt, 2019). Public health recommendations are often based on evidence that is weaker due to reliance on non-randomized, non-experimental studies. Guidance development in the public health sphere will necessarily need to be more interdisciplinary compared to other guidelines and may face additional challenges reaching consensus among diverse stakeholders (Hilton Boon et al., 2021). Political contexts may complicate consensus in public health guidelines (Hilton Boon et al., 2021). Regardless of these additional barriers, public health interventions have the potential to improve the health and wellbeing of populations, and guidance is instrumental to ensure consistent, high quality service provision (Hilton Boon et al., 2021). The GRADE framework supports providing strong recommendations based on low or very low evidence, as is often the case in public health (Hilton Boon et al., 2021). We experienced the additional challenge of developing public health guidance during an evolving public health emergency; we cannot wait for the generation of further published evidence while people are dying.

We included gaps in knowledge for all three of our recommendations with the aim of encouraging more high-quality research in collaboration with communities of people who use drugs.

Disseminating and Implementing Recommendations

After publication of the guidance document, we will circulate the report to all Naloxone Guidance Development Group members for dissemination to their respective networks, partner organizations that may have been unable to participate in guidance development, and all relevant governmental bodies responsible for naloxone distribution.

We have included as much information as possible about source documents so that programs can investigate how to implement or adapt these recommendations in their areas of practice.

Facilitators and Barriers to Implementation

A key facilitator to the implementation of this guidance is the Naloxone Guidance Development Group. We were fortunate to work with these diverse, dedicated individuals from across the country with the shared goal of informing high-quality harm reduction services. We

undertook this collaboration to address current priorities in THN programs in Canada and to reflect the real-world challenges encountered by those distributing naloxone and providing training on overdose response. Additionally, we hope that the Naloxone Guidance Development Group will bring some of the information generated in this guidance document to their home organizations.

Throughout the guidance development process, the Naloxone Guidance Development Group discussed how limited resources interfered with the ability to provide intranasal naloxone and to support further overdose response training. We hope to see further investment in this life saving intervention and in harm reduction in general.

While the recommendation on kit contents closely reflects current Canadian THN kits, the recommendations on route of administration of will require political will and resources.

Limitations

A key limitation is that Newfoundland and Labrador, the Northwest Territories, Nunavut, and Prince Edward Island were not represented in the Naloxone Guidance Development Group despite targeted recruitment. During recruitment some nominees from these provinces and territories reported a higher than usual workload due to the COVID-19 pandemic as a barrier to participation. In order to address this gap, we increased our effort to engage people who use drugs and frontline harm reduction workers from these regions in the public input process.

NEXT STEPS

Procedure for Updating the Guidance

The funding for this project does not allow for updates to this guidance. We have published details on the questions that the Naloxone Guidance Development Group deemed important for inclusion in Canadian guidance (Ferguson et al., 2022) as well as details on the systematic review methods used to identify relevant published academic and grey literature evidence Appendix 2 in our published manuscript (Ferguson et al., In Press) so that new data can be easily identified.

CONCLUSION

This guidance development project sought to identify and address key questions on THN distribution. We generated recommendations on overdose response, kit contents, and routes of administration with the goal of improving standardized evidence-based practice and share community knowledge.

APPENDIX A: MANAGEMENT OF COMPETING INTERESTS

A conflicts of interest (COI) form was developed and distributed to committee members. Committee members were asked to disclose any financial, institutional, or intellectual conflicts of interest. Specifically, committee members were asked to disclose any potential conflicts and interests in employment & consulting, research support, Investment Interests, intellectual property, and public statements & positions. COIs were ascertained and independently screened by two members of the team (MF and JN or JB) for any potential conflicts.

The Guidelines International Network's Principles for Disclosure of Interests and Management of Conflicts was used as a framework in this guidance development project (Schünemann et al., 2015). Using this framework, each member was assessed quantitatively on a "relevance index" on a scale from 0 to 5 or assessed as "non-applicable". Of those associated with the project (including the leadership group, research team, and Naloxone Guidance Development Group), 18 had no interests declared and were "not applicable" on the scoring system. A total of 26 had declared interests deemed not relevant to the project and rated 0 on the relevance index. Research team members who were not involved with recommendation generation were not required to submit a conflict of interest form.

None of the project members were excluded from participation or had participation restricted due to direct financial conflict of interest. In 2012, JAB implemented BC's THN program and oversaw evaluations and research related to BC program as an employee of BC Centre for Disease Control. In 2015 and 2016, JAB was an invited presenter with covered travel costs for the Western Canada Additions Forum and National Opioid Crisis Summit and presented on the importance of naloxone. Three members reported relationships with corporations in the biomedical sphere. PL was an investigator on a study which received in-kind donation of intranasal naloxone; the pharmaceutical company has no role in the design or conduct of the research. AT's family member worked for a pharmaceutical company whose scope of work is unrelated to naloxone. BG received honoraria for speaking engagements totaling approximately $8000, and a loan of equipment for a clinical trial from a corporation that creates medical equipment not associated with naloxone. None of the disclosed potential indirect conflicts of interest or bias were deemed to be of sufficient relevance or weight to warrant exclusion from the committee.

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