**Appendix 5: Systematic Review Methods**

# Table of Contents

## Additional Systematic Review Methods

If more than 1000 results were retrieved, a set of search terms representing the comparator was added to further limit the search for study feasibility. By not initially including the comparator and outcome search terms, we were able to broaden our findings (1).

Website selection was based on CADTH's 'Grey Matters' checklist and technical guidance from the harm reduction literature (Canadian Agency for Drugs and Technologies in Health [CADTH], 2015). Websites searched included Guidelines International Network (GIN); Grey Guide: Repository and Portal to Good Practices and Resources in Grey Literature; Google (first five pages of results); government websites in Canada, the United States, Europe, and Australia; and the websites of the WHO, the United Nations, the Canadian Centre on Substance Use and Addiction (CCSA), and the Canadian Agency for Drugs and Technology in Health (CADTH).

We conducted a search for Canadian provincial or territorial guidelines using the search terms "[name of all provinces and territories]" "guideline" and "naloxone" and searched the first three pages of results.

After completing searches of the peer-reviewed and grey literature, we conducted backward and forward citation chaining. Backward citation chaining consists of screening the references of included articles, whereas forward citation chaining entails screening articles citing the included article. We also contacted subject matter experts to identify additional relevant citations.

Study data were collected and managed using REDCap electronic data capture tools hosted at the University of British Columbia (2,3). The research team developed and piloted the data collection form.

The Synthesis Without Meta-Analysis reporting guideline tool (SWiM) was used to guide analysis of data inappropriate for meta-analysis (4).

Table 1: Research Questions

| 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? |

Table 2: PICOS Breakdown of Health Questions

| | Population/Problem | Intervention/ Exposure | Comparison | Outcome/Findings | Healthcare Setting/Context |
|---|---|---|---|---|---|
| **Route of Administration** | Adults and mature minors (13 years and over) experiencing overdose | Intranasal route of administration for naloxone | Intramuscular route of administration for naloxone<br><br>or<br><br>No comparison | Morbidity (including but not limited to anoxic brain injury, pulmonary edema, etc.) and mortality | In community setting outside of a professional role. |
| **Kit Contents** | Adults and mature minors (13 years and over) experiencing overdose in community setting or responding to overdose | Naloxone kit distribution at the community level | Kit contents<br><br>or<br><br>No comparison | Included but not limited to infection control, preference, or health outcomes (morbidity, mortality) | In community setting outside of a professional role. |

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

Table 3 Dates of Literature Searches

|  | Overdose Response | Kit Contents | Route of Administration |
|---|---|---|---|
| Scientific Literature<br>    Medline<br><br>    EMBASE<br><br>    CINAHL<br><br>    PsycInfo<br><br>    Cochrane Central Register of Controlled Trials<br><br>    Cochrane Database of Systematic Reviews<br><br>    Epistemonikos | May 31-June 3 2022 | May 31-June 23, 2021 | October 15-18, 2021 |

| Funding Databases and Proposals<br>PROSPERO<br><br>NiH RePORT<br><br>CIHR Funding Decisions | February 17-25, 2022 | February 17-25, 2022 | February 17-25, 2022 |
|---|---|---|---|
| Grey Literature | July 30-August 3, 2021 | July 25-December 2 2021 | July 30, 2021 |

Table 4 Routes of Administration Search Strategy

| Database | POPULATION/PROBLEM<br>People experiencing overdose | INTERVENTION/EXPOSURE<br>Naloxone administration | COMPARATOR<br>Intranasal or intramuscular routes of administration | OUTCOMES/FINDINGS<br>Mortality and morbidity (including but not limited to anoxic brain damage, pulmonary edema, etc. |
|---|---|---|---|---|
| Ovid Medline | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kf | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kf | exp Drug Administration Routes/ OR Naloxone/ad OR (nasal OR intranasal OR intramuscular OR intra-muscular OR formulation? OR injectable OR injector? OR dosage? OR repeat* OR titrat*).ti,ab,kf | Not required (P + I + C = <1000 results) |
| EMBASE | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kw | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kw | exp Drug Administration Routes/ OR Naloxone/ad OR (nasal OR intranasal OR intramuscular OR intra-muscular OR formulation? OR injectable OR injector? OR dosage? OR repeat* OR titrat*).ti,ab,kw. | Morbidity/<br>Mortality/<br>Mortality rate/<br>Survival/<br>Brain Injury/<br>Brain Damage/<br>Brain Hypoxia/<br>Pulmonary Edema/<br>Naloxone/ae<br>Narcotic Antagonists/ae<br>Adverse event/ |

|  |  |  |  | OR<br><br>(morbidity OR mortality OR survival OR "brain damage" OR "brain injury" OR hypoxi? OR "pulmonary edema" OR "pulmonary oedema" OR sequelae OR complication? OR adverse).ti,ab,kw |
|---|---|---|---|---|
| CINAHL | MH Overdose OR (TI(overdos* OR poison* OR toxicity OR intoxicat*)) OR (AB(overdos* OR poison* OR toxicity OR intoxicat*)) | MH(Naloxone OR Narcotic Antagonists) OR (TI (naloxone OR narcan OR "opiate antagonist#" OR "opioid antagonist#" OR "narcotic antagonist#")) OR (AB (naloxone OR narcan OR "opiate antagonist#" OR "opioid antagonist#" OR "narcotic antagonist#")) | MH(Drug Administration Routes or Naloxone/ad) or TI(nasal or intranasal or intramuscular or intra-muscular or formulation# or injector# or dosage# or repeat* or titrat*) or AB(nasal or intranasal or intramuscular or intra-muscular or formulation# or injector# or dosage# or repeat* or titrat*) | Not required (P + I + C = <1000 results) |
| PsycINFO | DE(Drug Overdoses) OR MA(Drug Overdose) OR (AB(overdos* OR poison* OR toxicity OR intoxicat*)) OR (TI(overdos* OR poison* OR toxicity OR intoxicat*)) | DE(Naloxone) OR DE(Narcotic Antagonists) OR MA(Naloxone) OR MA(Narcotic Antagonists) OR (AB(naloxone OR narcan OR "opiate antagonist*" OR "opioid antagonist*" OR "narcotic antagonist*")) OR (TI(naloxone OR narcan OR "opiate antagonist*" OR "opioid antagonist*" OR "narcotic antagonist*")) | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Epistemonikos | overdos* OR poison* OR toxicity OR intoxicat* (title/abstract) | naloxone OR narcan OR "opiate antagonist" OR "opiate antagonists" OR "opioid antagonist" OR "opioid | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |

| | | antagonists" OR "narcotic antagonist" OR "narcotic antagonists" (title/abstract) | | |
|---|---|---|---|---|
| Cochrane Central Register of Controlled Trials | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kw | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kw | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Cochrane Database of Systematic Reviews | Drug Overdose.kw OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab | Naloxone.kw OR Narcotic Antagonists.kw OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |

Table 5: Kit Contents Search Strategy

| PICO Elements | Overdose response | Naloxone kit distribution | Kit contents | Health outcomes post overdose |
|---|---|---|---|---|
| MEDLINE | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kf | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kf | "Equipment and Supplies"/ OR Personal Protective Equipment/ OR (supplies OR content? OR PPE OR equipment OR kit OR kits OR ampul* OR ampoule? OR glove* OR needle? OR mask? OR barrier? OR shield? OR pamphlet?).ti,ab,kf | Not required (P + I + C = <1000 results) |
| EMBASE | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kw | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kw | "Equipment and Supplies"/ OR Personal Protective Equipment/ OR (supplies OR content? OR PPE OR equipment OR kit OR kits OR ampul* OR ampoule? OR glove* OR needle? OR mask? OR barrier? OR shield? OR pamphlet?).ti,ab,kw | Not required (P + I + C = <1000 results) |
| CINAHL | MH Overdose  OR (TI(overdos* OR poison* OR toxicity OR intoxicat*)) OR | MH Naloxone OR MH Narcotic Antagonists OR (TI (naloxone OR narcan OR "opiate antagonist#" OR "opioid | MH "Equipment and Supplies" OR MH Personal Protective Equipment OR (TI (supplies OR content# OR PPE OR | Not required (P + I + C = <1000 results) |

| | | | | |
|---|---|---|---|---|
| | (AB(overdos* OR poison* OR toxicity OR intoxicat*)) | antagonist#" OR "narcotic antagonist#")) OR (AB (naloxone OR narcan OR "opiate antagonist#" OR "opioid antagonist#" OR "narcotic antagonist#")) | equipment OR kit OR kits OR ampul* OR ampoule# OR glove* OR needle# OR mask# OR barrier# OR shield# OR pamphlet#)) OR (AB (supplies OR content# OR PPE OR equipment OR kit OR kits OR ampul* OR ampoule# OR glove* OR needle# OR mask# OR barrier# OR shield# OR pamphlet#)) | |
| PsycINFO | DE(Drug Overdoses) OR MA(Drug Overdose) OR (AB(overdos* OR poison* OR toxicity OR intoxicat*)) OR (TI(overdos* OR poison* OR toxicity OR intoxicat*)) | DE(Naloxone) OR DE(Narcotic Antagonists) OR MA(Naloxone) OR MA(Narcotic Antagonists) OR (AB(naloxone OR narcan OR "opiate antagonist*" OR "opioid antagonist*" OR "narcotic antagonist*")) OR (TI(naloxone OR narcan OR "opiate antagonist*" OR "opioid antagonist*" OR "narcotic antagonist*")) | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| PROSPERO | (MeSH DESCRIPTOR Drug Overdose EXPLODE ALL TREES) OR (overdos* OR poison* OR toxicity OR intoxicat*) | (MeSH DESCRIPTOR Naloxone) OR (MeSH DESCRIPTOR Narcotic Antagonists) OR (naloxone OR narcan OR opiate antagonist* OR opioid antagonist* OR narcotic antagonist*) | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Epistemonikos | overdos* OR poison* OR toxicity OR intoxicat* | naloxone OR narcan OR "opiate antagonist" OR "opiate antagonists" OR "opioid antagonist" OR "opioid antagonists" OR "narcotic antagonist" OR "narcotic antagonists" | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Cochrane Central Register of Controlled Trials | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kw | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kw | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Cochrane Database of Systematic Reviews | Drug Overdose.kw OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab | Naloxone.kw OR Narcotic Antagonists.kw OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |

Table 6: Overdose Response Search Strategy

| PICO Elements | Persons experiencing overdose | Naloxone response | Performing rescue breathing/ventilation vs. chest compressions | Health outcomes post overdose |
|---|---|---|---|---|
| MEDLINE | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kf | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kf | First Aid/ OR Cardiopulmonary Resuscitation/ OR Respiration, Artificial/ OR (CPR OR cardiopulmonary OR compress* OR "rescue breath*" OR respiration? OR ventilat* OR mouth-to-mouth).ti,ab,kf. | Not required (P + I + C = <1000 results) |
| EMBASE | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kw | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kw | First Aid/ OR Cardiopulmonary Resuscitation/ OR Respiration, Artificial/ OR (CPR OR cardiopulmonary OR compress* OR "rescue breath*" OR respiration? OR ventilat* OR mouth-to-mouth).ti,ab,kw. | Not required (P + I + C = <1000 results) |
| CINAHL | MH Overdose OR (TI(overdos* OR poison* OR toxicity OR intoxicat*)) OR (AB(overdos* OR poison* OR toxicity OR intoxicat*)) | MH Naloxone OR MH Narcotic Antagonists OR (TI (naloxone OR narcan OR "opiate antagonist#" OR "opioid antagonist#" OR "narcotic antagonist#")) OR (AB (naloxone OR narcan OR "opiate antagonist#" OR "opioid antagonist#" OR "narcotic antagonist#")) | MH(Bystander CPR OR Resuscitation, Cardiopulmonary OR First Aid OR Respiration, Artificial) OR TI(CPR OR cardiopulmonary OR compress* OR "rescue breath*" OR respiration# OR ventilat* OR "mouth-to-mouth") OR AB(CPR OR cardiopulmonary OR compress* OR "rescue breath*" OR respiration# OR ventilat* OR "mouth-to-mouth") | Not required (P + I + C = <1000 results) |
| APA PsycINFO | DE(Drug Overdoses) OR MA(Drug Overdose) OR (AB(overdos* OR poison* OR toxicity OR intoxicat*)) OR (TI(overdos* OR poison* OR toxicity OR intoxicat*)) | DE(Naloxone) OR DE(Narcotic Antagonists) OR MA(Naloxone) OR MA(Narcotic Antagonists) OR (AB(naloxone OR narcan OR "opiate antagonist*" OR "opioid antagonist*" OR "narcotic | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |

| | | | | |
|---|---|---|---|---|
| | | antagonist*")) OR (TI(naloxone OR narcan OR "opiate antagonist*" OR "opioid antagonist*" OR "narcotic antagonist*")) | | |
| PROSPERO | (MeSH DESCRIPTOR Drug Overdose EXPLODE ALL TREES) OR (overdos* OR poison* OR toxicity OR intoxicat*) | (MeSH DESCRIPTOR Naloxone) OR (MeSH DESCRIPTOR Narcotic Antagonists) OR (naloxone OR narcan OR opiate antagonist* OR opioid antagonist* OR narcotic antagonist*) | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Epistemonikos | overdos* OR poison* OR toxicity OR intoxicat* | naloxone OR narcan OR "opiate antagonist" OR "opiate antagonists" OR "opioid antagonist" OR "opioid antagonists" OR "narcotic antagonist" OR "narcotic antagonists" | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Cochrane Central Register of Controlled Trials | Drug Overdose/ OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab,kw | Naloxone/ OR Narcotic Antagonists/ OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab,kw | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |
| Cochrane Database of Systematic Reviews | Drug Overdose.kw OR (overdos* OR poison* OR toxicity OR intoxicat*).ti,ab | Naloxone.kw OR Narcotic Antagonists.kw OR (naloxone OR narcan OR "opiate antagonist?" OR "opioid antagonist?" OR "narcotic antagonist?").ti,ab | Not required (P + I = <1000 results) | Not required (P + I = <1000 results) |

1. Frandsen TF, Bruun Nielsen MF, Lindhardt CL, Eriksen MB. Using the full PICO model as a search tool for systematic reviews resulted in lower recall for some PICO elements. J Clin Epidemiol. 2020 Nov;127:69–75.

2. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019 Jul;95:103208.

3. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377–81.

4. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ. 2020 Jan 16;l6890.