Appendix 3: Systematic Review Findings

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Routes of Administration

Figure 1: Routes of Administration - PRISMA diagram

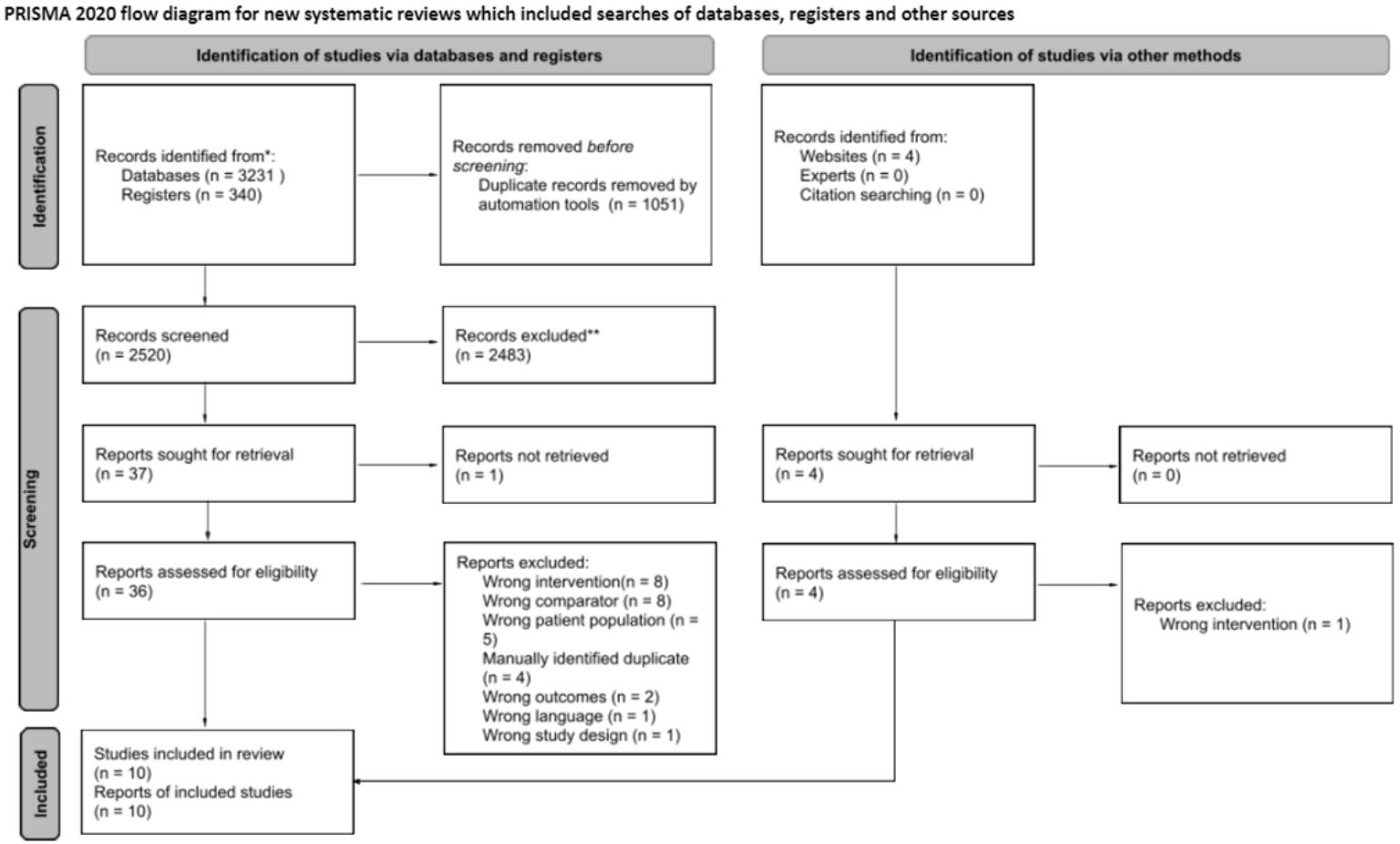

Table 1: Route of Administration - Study description and PICO elements of included sources

Citation	Study Design	Objective	Population/Problem	Intervention/Exposure	Comparator	Outcomes/Findings
Chou et al., 2017	Systematic review	"To synthesize evidence on 1) the effects of naloxone route of administration and dosing for suspected opioid overdose in out-of-hospital settings on mortality, reversal of overdose, and harms, and 2) the need for transport to a health care facility after reversal of overdose with naloxone." (p. 867)	"Patients with confirmed or suspected opioid overdose in out-of-hospital settings" (p 868)	Administration of naloxone via nasal route	Administration of naloxone via intramuscular route (of note: review compared other routes of administration including intravenous and subcutaneous injection but evidence was insufficient to evaluate)	"Outcomes were mortality, reversal of overdose symptoms, time to reversal of symptoms, recurrence of symptoms, cardiac or respiratory arrest, other clinical sequelae of overdose, function, quality of life, health care use, and harms" (p 868)
Health Technology Assessment Unit, 2020	Grey literature (health technology assessment)	"The primary research objectives of this HTA [health technology assessment] were to determine: 1. The clinical	"Subjects with opioid overdose" (p. 23)	"Administration of nasal naloxone" (p. 23)	"Administration of another naloxone formulation or placebo" (p. 23)	"Clinical outcomes may include but are not limited to: ● Time to adequate response ● Change in level of consciousness

		effectiveness of IN naloxone compared to intramuscular (IM) and intravenous (IV) naloxone [. . .]" (p. 10)				● Vital signs ● Arterial blood oxygen saturation" (p. 23)
Lewis et al., 2017	Narrative review	"to provide a historical context for the development of IN naloxone and related strategies for the treatment of opioid overdoses, in addition to an assessment of the current status of this area." (p. 80)	"Treatment of opioid overdoses in patients by laypeople in a community setting" (abstract)	"IN naloxone kit for community use by medically untrained first responders" (p 80)	"Intramuscular (IM) naloxone autoinjector for layperson use" (p 80)	"Morbidity and mortality in community settings" (p 81) No outcomes explicitly stated but does discuss overdose-related morbidity and mortality More generally: to "review the current and historical literature..." and show "what work needs to be done to integrate these programs into efforts to provide effective treatment of opioid use disorders" (abstract)

Mueller et al., 2015	Systematic review	"to review and classify existing publications on OEND and naloxone in community-based settings. We sought to identify evidence of effectiveness and opportunities for translation of these practices into conventional medical settings." (p. 242)	“Naloxone administration [of patients] in prehospital settings” (p 242)	In relation to SR3: The safety, convenience, and effectiveness of the intranasal route of administration (p 249) (see table 1 if need specific information on studies)	In relation to SR3: The safety convenience and effectiveness of the intranasal route in comparison with IM naloxone (p 249)	More generally: “For this review, we summarized and classified existing publications on overdose education and naloxone distribution to identify evidence of effectiveness and opportunities for translation into conventional medical settings.”
Peprah & Frey, 2017	Grey literature (rapid review[1])	“to provide evidence on the comparative clinical effectiveness and cost effectiveness of the various formulations and delivery mechanisms of naloxone for the treatment of opioid poisoning" (p. 5)	“Patients (of any age) suspected of opioid overdose in the pre-hospital setting” Subgroups of interest: “pediatric (< or = 18 years of age) and adult (>18 years of age) populations, pregnant, and lactating, geriatric” (p 7, table 2)	In relation to SR3 Clinical effectiveness of naloxone hydrochloride nasal spray clinical effectiveness of naloxone administered intranasally using a mucosal atomizer	Clinical effectiveness of intramuscular naloxone	“Clinical effectiveness: (e.g., proportion of patients with an adequate response within 10 minutes of administration, change in level of consciousness, time to adequate response, hospitalization, requirement for rescue naloxone due to inadequate

						primary response, vital signs, arterial blood oxygen saturation); Harms: (e.g., drug-related adverse events; frequency of adverse events, opioid withdrawal effects, including acute opioid withdrawal syndrome, length and severity of withdrawal, length of hospital stay; cardiovascular side-effects; administration-related adverse events such needle site reactions and needle stick injury; study-related side-effects [e.g., agitation]; and rebound opioid toxicity)" (p 7, table 2)

Peprah & Severn, 2019	Grey literature (rapid review[1])	"In 2017, CADTH produced a Rapid Response report summarizing evidence on the comparative clinical effectiveness, cost effectiveness, and evidence-based recommendations for use of the various formulations and delivery mechanisms of naloxone for the treatment of opioid poisoning in pre-hospital settiongs. The evidence available then for that report was limited in number and quality. Therefore, the objective of this current Rapid Response report is to review any new	Patients (of any age) suspected of opioid overdose in the pre-hospital setting -Subgroups of interest: pediatric (≤ 18 years of age) and adult (> 18 years of age) populations, pregnant and lactating, geriatric	Naloxone Hydrochloride Nasal Spray and naloxone administered intranasally using a mucosal atomizer	Intramuscular naloxone	"Clinical effectiveness: (e.g., proportion of patients with an adequate response within 10 minutes of administration, change in level of consciousness, time to adequate response, hospitalization, requirement for rescue naloxone due to inadequate primary response, vital signs, arterial blood oxygen saturation); Harms: (e.g., drug-related adverse events; frequency of adverse events, opioid withdrawal effects, including acute opioid withdrawal syndrome, length and severity of withdrawal, length of hospital stay; cardiovascular side-

		evidence that may have become available since the 2017 report and update the evidence." (p. 4)				effects; administration-related adverse events such needle site reactions and needle stick injury; study-related side-effects [e.g., agitation]; and rebound opioid toxicity)" (p 5, table 1)
Razaghizad et al., 2021	Umbrella review	"To conduct an umbrella review of systematic reviews to provide a broad-based conceptual scheme of the effect and feasibility of OEND [opioid education and naloxone distribution] and to identify areas for possible optimization." (p. e1)	"Most reviews did not specify their target population; participants of included studies were thus primarily self-identified persons who use heroin unless stated otherwise" (p e4)	Concentration of intranasal naloxone formulation	Concentration of intramuscular naloxone formulation	More generally: "naloxone safety and efficacy, knowledge improvement, bystander overdose response, overdose mortality, bystander naloxone efficacy, causality, feasibility of OEND implementation, optimal naloxone formulation, need for hospital transport after overdose rescue, public and participant attitudes" (see table 1, p e5)

Strang et al., 2019	Narrative review	To "provide the reader with the evidence for THN as a public health response to opioid overdose as well as presenting evidence on naloxone's properties and the recent development of novel naloxone formulations and devices for layperson use as well as exploring ongoing challenges for implementation" (p. 1396)	Not stated	Naloxone nasal spray	Intramuscular naloxone formulation	Opioid mortality
Weaver et al., 2018	Narrative review	"This article compares the various routes of administration of naloxone in an attempt to determine the	Routes of administration of naloxone for participants with opioid overdose	Intranasal naloxone formulation	Intramuscular naloxone formulation	Depending on study, either educational efficacy, or mortality/morbidity

		optimal route in the prehospital setting" (p. 92)				
WHO, 2014	Clinical guideline	"to reduce the number of deaths from opioid overdose by providing evidence-based recommendations on the availability of naloxone for people likely to witness an opioid overdose along with advice on the resuscitation and post-resuscitation care of opioid overdose in the community." (p. ix)	“People with opioid overdose in the community setting” (p 35)	“Use of intranasal route of administration of naloxone” (p 35)	“Use of intramuscular or subcutaneous route of administration of naloxone” (p 35)	“Overdose mortality, overdose complication, overdose morbidity, opioid withdrawal reaction to naloxone, time to administer naloxone, time to opioid overdose reversal, ease of administration, BBV transmission through unsafe injection, unsafe injection related injury, adverse effect of resuscitation, psychosocial intervention/referral to treatment post overdose” (p 35)

[1]CADTH identifies Peprah & Frey (2017) and Peprah & Severn (2019) as a class of “Rapid Response Report” called “summaries with critical appraisal. “The purpose of a Summary with Critical Appraisal is to quickly identify, appraise, and summarize existing evidence on specific health topics to provide evidence-based support to policy and health care decision-makers.” (CADTH, 2015, p. 5)

Table 1: Route of Administration - Quality of evidence table for outcomes reported

Population-important outcomes	Surrogate outcomes[1]	# of studies and study design[1]	Risk of bias based on PHO MetaQat	Inconsistency	Indirectness	Imprecision	Overall quality of evidence
Overdose-related mortality	Overdose reversal, reversal rate	3 studies 1 systematic review (Mueller et al., 2015) 1 umbrella review (Razaghizad et al., 2021) 1 rapid review (grey literature) (Peprah & Frey, 2017)	Unclear[3]	Low[4]	High[5]	High[6]	Very low.
	Need for supplemental naloxone	1 health technology assessment (grey literature) (HTAU, 2020)					
	Effectiveness, efficacy[11]	3 studies 2 narrative reviews (Lewis et al., 2017; Weaver et al., 2018) 1 systematic review (Chou et al., 2017)					
Overdose-related morbidity	Overdose morbidity[2]	1 clinical guideline (WHO, 2014)	Low[7]	None[8]	High[9]	Moderate[10]	Very low.

[1] Outcomes reported by included studies. Peprah and Frey (2017) reported reversal rate and need for supplemental naloxone. In accordance with GRADE guidance, only one outcome (reversal rate) was included.

[2] The WHO reports on “overdose morbidity” and states that “adequate response” was used as a surrogate measure (see “Summary of Findings Table”, p. 43, footnote 7).

[3] Not downgraded. Most information is from studies at low or unclear risk of bias.

[4] Not downgraded. Differences in direction of effect are present, but differences in estimated size of effect appear small.

[5] Downgraded. No studies of community overdose responder administration were identified by the included studies; surrogate measures are imperfect measures of overdose-related mortality.

[6] Downgraded. Studies do not provide estimates of effect.

[7] Not downgraded. Information is from a study at low risk of bias.

[8] Not downgraded. Only one study identified.

[9] Downgraded. No studies of community overdose responder administration administration were identified by the included studies; a proxy measure (adequate response) was used for overdose morbidity.

[10] Downgraded. Total sample size in meta-analysis is < 400.

[11]Chou et al. (2017), Lewis et al. (2017), and Weaver et al. (2018) drew conclusions on general “efficacy” or “effectiveness”. Chou et al. (2017) state that efficacy is based on “likelihood of an adequate response, time to reversal, and recurrence of symptoms” (p. 871). Lewis et al. (2017) and Weaver et al. (2018) do not explicitly define efficacy/effectiveness, but reviewed evidence on response rate, time to response, and need for rescue naloxone.

xx: Chou et al. (2017) report “efficacy” based on “likelihood of an adequate response, time to reversal, and recurrence of symptoms” (p. 871). Mueller et al. (2015) report “effectiveness”

Kit Contents

Figure 2: Kit Contents - PRISMA diagram

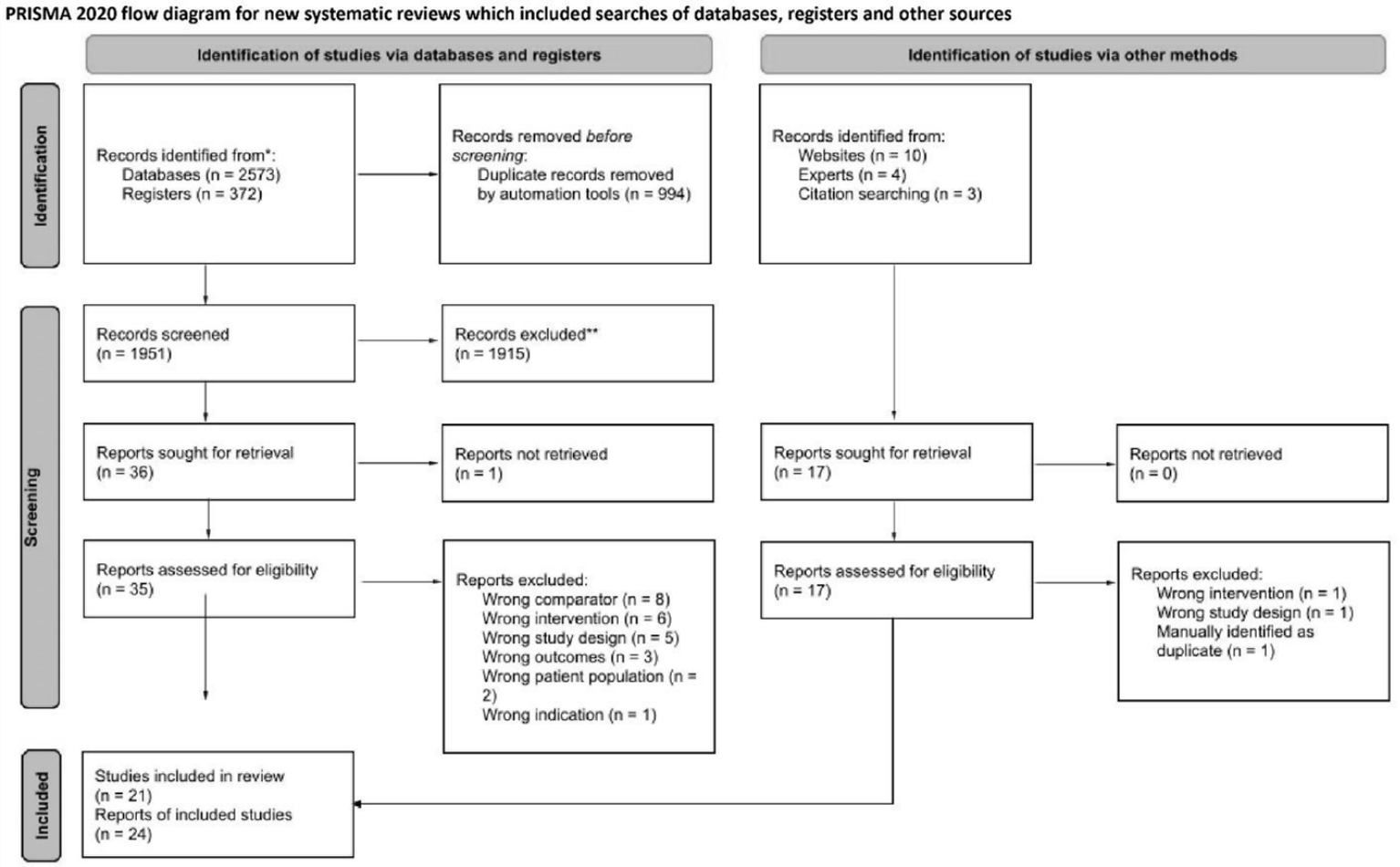

Table 3: Kit Contents - Study description and PICO elements of included sources

Source (Country)	Study Type	Objective / Aim	Population / Problem	Intervention / Exposure	Comparator	Outcomes / Findings
Harvey, G. S., Knox, M., Hyshka, E., Rowe, A., Lefsrud, L., Sommerfeldt, S., & Forhan, M. (2021). Opioid overdose response and health information complexities: A pilot study on Naloxone kit design. *The Journal of Health Design*, *6*(2), 391–400. https://doi.org/10.21853/JHD.2021.135 (Canada)	Qualitative Research	"This research aims to identify and present opportunities in which design can provide insights for improving public health education, reducing stigma, and enhancing clarity in health messaging to influence the uptake of Naloxone kits among men who have experienced or encountered an opioid overdose scenario. It further examines the use of design methods and how they can be effective in creating health tools for specific populations." (p. 391)	“20 male participants between 18-40 years with a history of drug use and past or current enrolment in drug rehabilitation programs” (p 393)	Co-design of naloxone kits	N/A	The research team identified design factors that improved naloxone kit instructions and uncovered broader issues that hinder kit use.
Neale, J., Farrugia, A., Campbell, A. N., Dietze, P., Dwyer, R., Fomiatti, R., Jones, J. D., Comer, S. D., Fraser, S., & Strang, J. (2021). Understanding preferences for type of take-home naloxone device: International qualitative analysis of	Qualitative Research	"In this paper, we address a gap in the existing literature by exploring the preferences of people who use opioids for different THN devices. In so doing, our objective is to provide new insights that might help to inform the design and	Study 1: "the naloxone device preferences of people who use opioids"; Study 2: "Users of either non-medical/illicit or prescription opioids" (p. 3)	Naloxone administration devices	“Improvised multi-step atomized spray assembled by combining a luer-lock syringe of naloxone with a nasal atomizer” (table 1) “intramuscular device comprising a 22-gauge needle & syringe with a cylindrical glass vial of	Preferences for type of take-home naloxone device

the views of people who use opioids. *Drugs: Education, Prevention and Policy*, 1–12. https://doi.org/10.1080/09687637.2021.1872499 (Australia & USA)		development of future naloxone technology whilst also identifying the most appropriate devices for THN programs to acquire and distribute when resources permit." (p. 2)			(0.4 mg/1 ml) naloxone, where the vial was sealed with a rubber stopper & a cap that needed to be flipped off before use" "intramuscular device comprising a 22-gauge needle & syringe with a cylindrical glass vial of (0.4 mg/1 ml) naloxone, where the vial was sealed with a rubber stopper & a cap that needed to be flipped off before use" "naloxone ampoules for intramuscular use, where the ampoules were made of glass, had a sealed neck & were opened by snapping the top off the neck"	
Alberta Health Services Harm Reduction Services. (2020). *Community Based Naloxone Program Opioid Poisoning Response Curriculum Guide For Trainers* (p. 46). Alberta Health Services Harm Reduction Services. https://www.albertah	Grey Literature (Curriculum to support naloxone kit providers)	"[…] the purpose of this curriculum is to provide information, background, and rationale for people who will be providing opioid poisoning response training and/or community based naloxone kit distribution in Alberta [. . .]" (p. 3)	N/A (intended to support trainers and naloxone kit providers (p 5)	N/A (discusses naloxone kit distribution)	N/A	N/A

ealthservices.ca/assets/info/hrs/if-hrs-cbn-opioid-poisoning-response-curriculum-guide.pdf (Canada)						
Alberta Health Services Harm Reduction Services. (2020). *Intramuscular and Nasal Naloxone Administration: Suspected Opioid Poisoning (Overdose) Decision Support Tool* (p. 16). https://www.albertahealthservices.ca/assets/info/hrs/if-hrs-im-nasal-naloxone-administration-opioid-poisoning-dst.pdf (Canada)	Grey Literature (Decision Support Tool)	"This Decision Support Tool (DST) is intended to support the Naloxone Administration: Suspected Opioid Poisoning (Overdose) Policy. This policy enables Alberta Health Services (AHS) staff to administer naloxone in response to a suspected opioid poisoning (overdose) in an emergency situation within AHS settings." (p. 2)	N/A (Intended to support Alberta Health Services staff)	N/A (Decision making support on naloxone administration)	N/A	N/A
Cohen, B. R., Mahoney, K. M., Baro, E., Squire, C., Beck, M., Travis, S., Pike-McCrudden, A., Izem, R., & Woodcock, J. (2020). FDA Initiative for Drug Facts Label for Over-the-Counter Naloxone. *New England Journal of Medicine*, *382*(22), 2129–2136.	Mixed Methods Research	"To address industry-perceived barriers to such access [over-the-counter access to naloxone], the Food and Drug Administration (FDA) developed a model drug facts label for such sales to assess whether consumers understood the key statements for safe	"adults who had recently used opioids (prescription opioids, heroin, or both) and their family and friends, the general population of adults who had not been screened for opioid use, and the general population of adolescents 15 to 17 years of age who had	Over-the counter drug facts label ("primary means through which instructions for safe and effective use are conveyed to consumers" (p2130))	FDA-created model label for facilitating appropriate use of naloxone ("one was adapted for the use of a nasal spray and one for the use of an autoinjector" (p 2131)	Label comprehension

https://doi.org/10.1056/NEJMsa1912403 (USA)		and effective use [of naloxone]." (p. 2129)	not been screened for opioid use" (p 2131)			
College of Pharmacists of Manitoba. (2020). *Naloxone: Frequently Asked Questions*. https://cphm.ca/wp-content/uploads/Resource-Library/Naloxone/Naloxone-FAQ-MB.pdf (Canada)	Grey Literature	Not stated, but document is an FAQ on naloxone and is aimed at pharmacists.	Individuals who may benefit from a THN kit	N/A	N/A	N/A
Eggleston, W., Calleo, V., Kim, M., & Wojcik, S. (2020). Naloxone Administration by Untrained Community Members. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *40*(1), 84–88. https://doi.org/10.1002/phar.2352 (USA)	Randomized Controlled Trial	"Although community members who complete naloxone training are able to administer nasal naloxone successfully and rapidly, little is known about the ability of community members to administer naloxone without training. The objective of this study was to assess the ability of untrained individuals to administer naloxone successfully in a simulated opioid overdose setting." (p. 84)	Healthy adults at least 18 years of age with no previous experience with naloxone administration or training	Naloxone kit distribution to participants and naloxone administration (p 85)	Kit contents (which includes one with a nasal spray, an intramuscular kit, or an improvised nasal atomizer kit) (p 85)	Successful administration, median time to successful administration and perceived usability of the device (p 86)

Harvey, G. S. (2020, April 28). *Take Home Naloxone Kit*. Take Home Naloxone Kit. https://www.designtosavelives.com/post/day-to-night-in-5-easy-steps (Canada)	Grey Literature (Blog post)	Not stated	“students, experienced drug users, and inexperienced friends and family of drug users” (no page number)	Distribution of drug overdose prevention kits	Redesigned and tested instructions and provincial overdose kits	Usability and accessibility of education and instructions
Harvey, G. S., & Bubric, K. (2020). *Information Design to Save Lives: Visualizing Data in the Design of Overdose Kits*. *12423*. https://doi.org/10.1007/978-3-030-60114-0 (Canada)	Mixed Methods Research	"to improve the design of instructions for how to use naloxone kits" (p. 402)	"Participants included individuals who had used opioids and those who had not. The sample also included a mix of individuals who had used a naloxone kit and those who had not." (p 406)	Naloxone Kits and instructions (p 403)	Redesigned Community Based Naloxone Kit instructions (p 403)	Usability and comprehension of instructions
Lai, J. T., Chapman, B. P., Carreiro, S. P., Babu, K. M., Boyer, E. W., & Chai, P. R. (2020). Understanding Naloxone Uptake from an Emergency Department Distribution Program Using a Low-Energy Bluetooth Real-time Location System. *Journal of Medical Toxicology*, *16*(4), 405–415. https://doi.org/10.1007/s13181-020-00774-8	Mixed Methods Research	"This study gauges acceptance of naloxone use and monitoring technology among people who use drugs (PWUD), and explores the use of real-time location systems (RTLS) in monitoring naloxone movements." (p. 405)	“adult patients aged 18 years or older who presented to our academic, urban ED with an opioid-related chief complaint (e.g. overdose, request for detoxification program, opioid withdrawal” (p 407)	Naloxone kit equipped with a low-energy Bluetooth (BLE) tracking system	N/A	Acceptance of naloxone use and monitoring technology to determine community penetrance of naloxone.

(USA)						
Lintzeris, N., Monds, L. A., Bravo, M., Read, P., Harrod, M. E., Gilliver, R., Wood, W., Nielsen, S., Dietze, P. M., Lenton, S., Shanahan, M., Jauncey, M., Jefferies, M., Hazelwood, S., Dunlop, A. J., Greenaway, M., Haber, P., Ezard, N., & Malcom, A. (2020). Designing, implementing and evaluating the overdose response with take-home naloxone model of care: An evaluation of client outcomes and perspectives. *Drug and Alcohol Review*, *39*(1), 55–65. https://doi.org/10.1111/dar.13015 (Australia)	Mixed Methods Research	To "1. develop, implement and evaluate a model of THN- BI suited to the target population and service settings; 2. examine the effectiveness of THN-BI in enhancing overdose-related knowledge, attitudes and behav- iours in clients; 3. examine the effectiveness of clinical procedures and health worker training programs in enabling workers to effectively deliver THN-BI; 4. examine client and health worker perspectives regarding THN interventions, barriers and enablers of THN uptake." (p. 56)	"High-risk opioid users attending alcohol & other drug treatment programs, needle & syringe programs, and health services for people who inject drugs in New South Wales."	Overdose response with take-home naloxone intervention	Not explicitly stated but discusses consumer perspectives and preferences of naloxone kits (table 5)	Effectiveness of program at enhancing knowledge, attitudes, and behaviors. Examine perspectives regarding THN interventions, barriers, and enables of THN uptake
Rowe, A., Knox, M., & Harvey, G. S. (2020). Re-thinking health through design: Collaborations in research, education and practice. Design for Health, 4(3), 327–344.	Mixed Methods Research	"In this article, we make the case for further opportunities for design and health to work together in deep, innovative and human ways." "We build upon shared histories, practices,	"audiences familiar with drug use" (p 336)	N/A (design as an interventionary tool to improve medical instructions in naloxone kits)	N/A	For project three (of three projects discussed): patient comprehension and improved performance and better information delivery

https://doi.org/10.1080/24735132.2020.1841918 (Canada)		knowledge gaps and goals through a discussion of three research projects that employ design practices within healthcare contexts. These experiments differ deliberately in scale and scope-from borrowing other disciplinary methods for designed environments-to developing curricular programs that apply design thinking to pressing health issues" Otherwise not explicitly stated for specific question (project 3 - p 335)				
Gottlieb, S. (2019). *Statement from FDA Commissioner Scott Gottlieb, M.D., on unprecedented new efforts to support development of over-the-counter naloxone to help reduce opioid overdose deaths*. FDA. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-unprecedented-new-	Grey Literature (Statement from FDA)	"To encourage drug companies to enter the OTC market and increase access to naloxone, the FDA took an unprecedented step: we developed a model DFL with easy-to-understand pictograms on how to use the drug. We also conducted label comprehension testing to ensure the instructions were simple to follow." (para. 6).	"a wide range of potential OTC naloxone users [including] people who use heroin; people who use prescription opioids; family and friends of people who use opioids; adolescents; and the general public." (para. 10).	Model drug facts label for naloxone kit with pictograms	N/A	Label comprehension from described study

efforts-support-development-over (USA)						
Moustaqim-Barrette, A., Elton-Marshall, T., Leece, P. N., Morissette, C., Rittenbach, K., & Buxton, J. (2019). *Environmental Scan Naloxone Access and Distribution in Canada*. The University of British Columbia. https://doi.library.ubc.ca/10.14288/1.0379400 (Canada)	Grey Literature (Environmental Scan)	"The current environmental scan was produced in order to better understand current practices and programs aimed to distribute naloxone for use in suspected opioid overdose, to assess uptake of these programs across Canadian provinces and territories (P/Ts), and to understand barriers related to knowledge and evidence in the use of naloxone, as well as operational obstacles to achieving widespread population coverage." (p. 5)	Canadians accessing naloxone	Naloxone distribution across Canadian provinces and territories (p 6)	N/A	Ascertain barriers to distribution of naloxone and management of opioid overdoses
Strang, J., McDonald, R., Campbell, G., Degenhardt, L., Nielsen, S., Ritter, A., & Dale, O. (2019). Take-Home Naloxone for the Emergency Interim Management of Opioid Overdose: The Public Health	Narrative Review	To "provide the reader with the evidence for THN as a public health response to opioid overdose as well as presenting evidence on naloxone's properties and the recent development	Adults experiencing overdose or responding to an overdose in the community setting	Naloxone kit distribution at the community level	N/A	Costs, legal barriers, effectiveness (see pg 1311-1413)

Application of an Emergency Medicine. *Drugs*, *79*(13), 1395–1418. https://doi.org/10.1007/s40265-019-01154-5 (Not applicable as source is a narrative review)		of novel naloxone formulations and devices for layperson use as well as exploring ongoing challenges for implementation" (p. 1396).				
Tippey, K. G., Yovanoff, M., McGrath, L. S., & Sneeringer, P. (2019). Comparative Human Factors Evaluation of Two Nasal Naloxone Administration Devices: NARCAN® Nasal Spray and Naloxone Prefilled Syringe with Nasal Atomizer. *Pain and Therapy*, *8*(1), 89–98. https://doi.org/10.1007/s40122-019-0118-0 (USA)	Qualitative Research	"For this study, we employed a systems-oriented human factors evaluation approach to deter-mine the differences in task complexity and risk between NARCAN Nasal Spray and a PFS-NA [prefilled syringe - nasal atomizer]." (p. 91).	N/A (no participants were engaged)	NARCAN Nasal Spray	Naloxone prefilled syringe with Nasal atomizer	Design and usability and use requirements
VandenBerg, S., Harvey, G. S., Martel, J., Gill, S., & McLaren, J. (2019, May 26). *Community based naloxone usability testing*. Annual Conference of the Canadian Association	Conference abstract	To "measure the effectiveness and usefulness of prototype community naloxone kit instructions over a six month period of time (2018) in Calgary and Edmonton with the	Not explicitly stated (described as voluntary participants)	Educational materials and instructions for community naloxone kits	Prototype instructions in naloxone kits	Effectiveness and usefulness of prototype community naloxone kit instructions

of Emergency Physicians, Halifax. (Canada)		aim to use human centred design principles to improve the way people interpret emergency overdose response directions." (p. S52)				
Canadian Mental Health Association Ontario. (2018). *Reducing Harms: Recognizing and Responding to Opioid Overdoses in Your Organization*. https://ontario.cmha.ca/wp-content/uploads/2018/05/CMHA-Ontario-Reducing-Harms-Updated.pdf (Canada)	Grey Literature (Guidance for Community Service Providers)	"The overarching goal of this resource is to equip community service providers with current, accessible and relevant information that can be used to inform and develop an opioid overdose protocol." (p. 3)	Community service providers	Naloxone administration and implementation of an overdose protocol	N/A	N/A
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/IN	Grey Literature (Guidance)	"to write a report on best practices in the area of resuscitation measures to be recommended to the general public in circumstances of naloxone administration." (p. 1).	Those responding to overdose	Overdose response and naloxone administration	N/A	N/A

ESSS/Rapports/Medicaments/INESSS_Avis_naloxone_RCR.pdf (Canada)						
Lai, J. T., Chapman, B. P., Boyle, K. L., Boyer, E. W., & Chai, P. R. (2018). *Low-energy Bluetooth for Detecting Real-world Penetrance of Bystander Naloxone Kits: A Pilot Study*. 3253–3258. https://doi.org/10.24251/HICSS.2018.411 (USA)	Observational study not otherwise specified	"The primary outcome for this study was demonstrating the feasibility of utilizing a BLE system to observe the transit of naloxone off a hospital campus. Secondary outcomes included observing the number of kits leaving the hospital campus and whether these kits were utilized by participants." (p. 5)	Participants presenting to the ED with an overdose or heroin-related complaint	Naloxone rescue kit with an integrated BLE beacon (p 2)		Community penetrance of ED distributed naloxone.
Pant, S., & Severn, M. (2018). *Funding and Management of Naloxone Programs in Canada*. Canadian Agency for Drugs and Technologies in Health. https://www.cadth.ca/sites/default/files/pdf/ES0319_funding_and_management_of_naloxone_programs_in_canada.pdf (Not applicable as source is a review)	Grey Literature (Environmental Scan)	"The purpose of this Environmental Scan is to present how naloxone is made available in Canadian provinces and territories. The key objectives are to answer the following questions: • How are take-home naloxone programs managed and funded? • How are take-home naloxone kits distributed? • What are the contents of	N/A	Funding and management of THN programs in Canada	NA	Summary of provincial/territorial funding

		publicly funded take-home naloxone kits? • How are public drug plans involved in the coverage and distribution of naloxone? • Which first responders carry and administer naloxone?" (p. 4)				
Lai, J. T., Chai, P., Boyle, K., & Boyer, E. (2017). Acceptance Among Heroin Users of Advanced Technology in Studying Naloxone Distribution Programs. *Journal of Medical Toxicology*, *13*, 3–46. https://doi.org/10.1007/s13181-017-0599-3 (USA)	Conference abstract	"to determine heroin users' acceptance of bystander naloxone kits and attitudes toward use of advanced technology to study the kits' community penetrance and geographic distribution patterns." (p. 13)	"Adults in the ED with a complaint related to heroin use" (p 13)	Naloxone kit distribution programs	"Advanced technology such as low-energy Bluetooth tracking beacons…'smart' naloxone kits" (p 13, 14)	Acceptance of bystander naloxone kits and attitudes toward use of advanced technology to study
Lai, J. T., Chai, P. R., Boyle, K. L., & Boyer, E. W. (2017). Use of technology to study bystander naloxone distribution. *Clinical Toxicology*, *55*, 371–544. https://doi.org/10.1080/15563650.2017.1309792 (USA)	Conference abstract	"to determine heroin users' acceptance of bystander naloxone kits and attitudes toward use of advanced technology to study the kits' community penetrance and geographic distribution patterns." (p. 453)	"Adults in the ED with a complaint related to heroin use" (p 453)	"Advanced technology such as low-energy Bluetooth tracking beacons…'smart' naloxone kits" (p 453)	N/A	Acceptance of advanced technology to study the efficacy of naloxone distribution programs

Orkin, A., Zlaiman, M. Z., Bingham, K., Leece, P. N., Hu, H., & Morrison, L. J. (2015, May). *Surviving opioid overdose with naloxone (SOON): Results of an international working group*. Canadian Journal of Emergency Medicine Annual Conference, Edmonton. (Canada)	Conference abstract	"To explore, through consensus opinion, ways to advance the practice, investigation, and implementation of bystander resuscitation and naloxone administration for opioid- associated resuscitative emergencies" (p. S76)	"The Surviving Opioid Overdose with Naloxone (SOON) Working Group, an international panel of expert and community stakeholders" (p. S76)	“1) rigorous research methodology to study the effectiveness of implementation strategies; 2) user-friendly delivery technologies; 3) standardized resuscitation and basic life support (BLS) guidelines in OARE; and 4) knowledge translation strategies to broaden access.” (p. S76)	N/A	“explore, through consensus opinion, ways to advance the practice, investigation, and implementation of bystander resuscitation and naloxone administration” (p S76)

Table 4: Kit Contents - Quality of evidence table for outcomes reported

Relevance to Kit Contents	Outcome(s)	# of studies and study design[1]	Risk of bias based on PHO MetaQat	Inconsistency	Indirectness	Imprecision	Overall quality of evidence
Choice of kit contents	Kit contents used in specific jurisdiction(s)	6 studies 6 grey literature (Alberta Health Services, 2020a, b; CMHA Ontario, 2018; College of Pharmacists of Manitoba, 2020; Jobin et al., 2018; Moustaqim-Barrette et al., 2019)	**Low** **Rationale**: Most information is from studies at low risk of bias. **Impact on quality:** Not downgraded	**Low** **Rationale:** There is minimal variation in kit contents across jurisdictions. **Impact on quality:** Not downgraded.	**Low** **Rationale:** Studies are directly relevant to the research question. **Impact on quality:** Not downgraded.	**Not applicable** **Rationale:** Studies are grey literature and/or qualitative and do not provide estimates of effect. **Impact on quality:** Not downgraded.	**Low.**
Choice of naloxone delivery device[1]	Expert opinions on delivery devices	2 studies 1 narrative review (Strang et al., 2019) 1 qualitative study (Orkin et al., 2015)	**Unclear** **Rationale**: Information is from studies at unclear risk of bias. **Impact on quality:** Not downgraded.	**Low** **Rationale:** Expert opinions do not conflict. **Impact on quality:** Not downgraded.	**Low** **Rationale:** Studies are directly relevant to the research question. **Impact on quality:** Not downgraded.	**Not applicable** **Rationale:** Studies are grey literature and/or qualitative and do not provide estimates of effect. **Impact on quality:** Not downgraded	**Low.**
	Rates of successful administration	1 randomized controlled trial (Eggleston et al., 2020)	**Low** **Rationale**: Information is from studies at low risk of bias. **Impact on quality:** Not downgraded	**Not applicable** **Rationale:** Only one study identified. **Impact on quality:** Not downgraded.	**Moderate** **Rationale**: The study used a simulated overdose scenario to assess rates of successful administration. However, it is thought unlikely that this would have a	**High** **Rationale:** Sample size is < 400; no estimates of effect. **Impact on quality:**	**Moderate.**

					significant impact on results. **Impact on quality:** Not downgraded.	Downgraded by one level.	
	User preference	2 studies 1 qualitative study (Neale et al., 2021) 1 mixed-methods study (Lintzeris et al., 2020)	**Low** **Rationale**: Information is from studies at low and high risk of bias. However, it is thought unlikely that the impact on this outcome would be significant. **Impact on quality:** Not downgraded	**Low** **Rationale:** Study findings are consistent. **Impact on quality:** Not downgraded..	**Low** **Rationale:** Studies are directly relevant to the research question. **Impact on quality:** Not downgraded.	**Not applicable** **Rationale:** Studies are qualitative/mixed-methods and do not provide estimates of effect. **Impact on quality:** Not downgraded	**Low.**
	Usability	1 qualitative study (Tippey et al., 2019)	**High** **Rationale**: Information is from a study at high risk of bias. **Impact on quality:** Downgraded one level.	**Not applicable** **Rationale:** Only one study identified. **Impact on quality:** Not downgraded.	**Low** **Rationale:** Study is directly relevant to the research question. **Impact on quality:** Not downgraded.	**Not applicable** **Rationale:** Study is qualitative and does not provide estimates of effect. **Impact on quality:** Not downgraded	**Very low.**
Instructions for use	User comprehension	6 studies 3 mixed methods (Cohen et al., 2020; Harvey & Bubric, 2020; Rowe et al., 2020)	**Unclear** **Rationale**: Most information is from studies at unclear risk of bias.	**High** **Rationale:** There is variability in study findings. This may be explained by differences in intervention (i.e. design and content of	**Moderate** **Rationale**: Most studies used a simulated overdose scenario to assess rates of successful administration. However, it is thought	**Not applicable** **Rationale:** Studies are grey literature and/or qualitative and do not provide estimates of effect.	**Low**.

		3 grey literature (Harvey, 2020; Gottlieb, 2019; VandenBerg et al., 2019)	**Impact on quality:** Not downgraded.	theinstructions for use). **Impact on quality:** Not downgraded	unlikely that this would have a significant impact on results. **Impact on quality:** Not downgraded.	**Impact on quality:** Not downgraded	
Inclusion of kit tracking technology	Feasibility	2 studies 1 observational study (Lai et al., 2018) 1 mixed methods study (Lai et al., 2020)	**Unclear** **Rationale**: Information is from studies at unclear risk of bias. **Impact on quality:** Not downgraded.	**Low** **Rationale:** Study findings are consistent. **Impact on quality:** Not downgraded.	**Low** **Rationale:** Studies are directly relevant to the research question. **Impact on quality:** Not downgraded.	**Not applicable** **Rationale:** Studies are grey literature and/or qualitative and do not provide estimates of effect. **Impact on quality:** Not downgraded	**Low.**
	Acceptability	4 studies 1 grey literature (Lai et al., 2017a) 2 observational studies (Lai et al., 2017b; Lai et al., 2018) 1 mixed methods study (Lai et al., 2020)	**Unclear** **Rationale**: Information is from studies at unclear risk of bias. **Impact on quality:** Not downgraded.	**Low** **Rationale:** Study findings are consistent. **Impact on quality:** Not downgraded.	**Moderate** **Rationale:** It is uncertain whether the views of the small number of study participants are applicable to our study population. **Impact on quality:** Downgraded one level.	**Not applicable** **Rationale:** Studies are grey literature and/or qualitative and do not provide estimates of effect. **Impact on quality:** Not downgraded level	**Very low**.
[1]Only comparisons of devices designed for the same route of administration (e.g. intramuscular, intranasal) are included. Comparisons of devices intended for different routes of administration (e.g. syringes vs. nasal spray) are excluded.							

Overdose Response

Figure 3: Overdose Response - PRISMA diagram

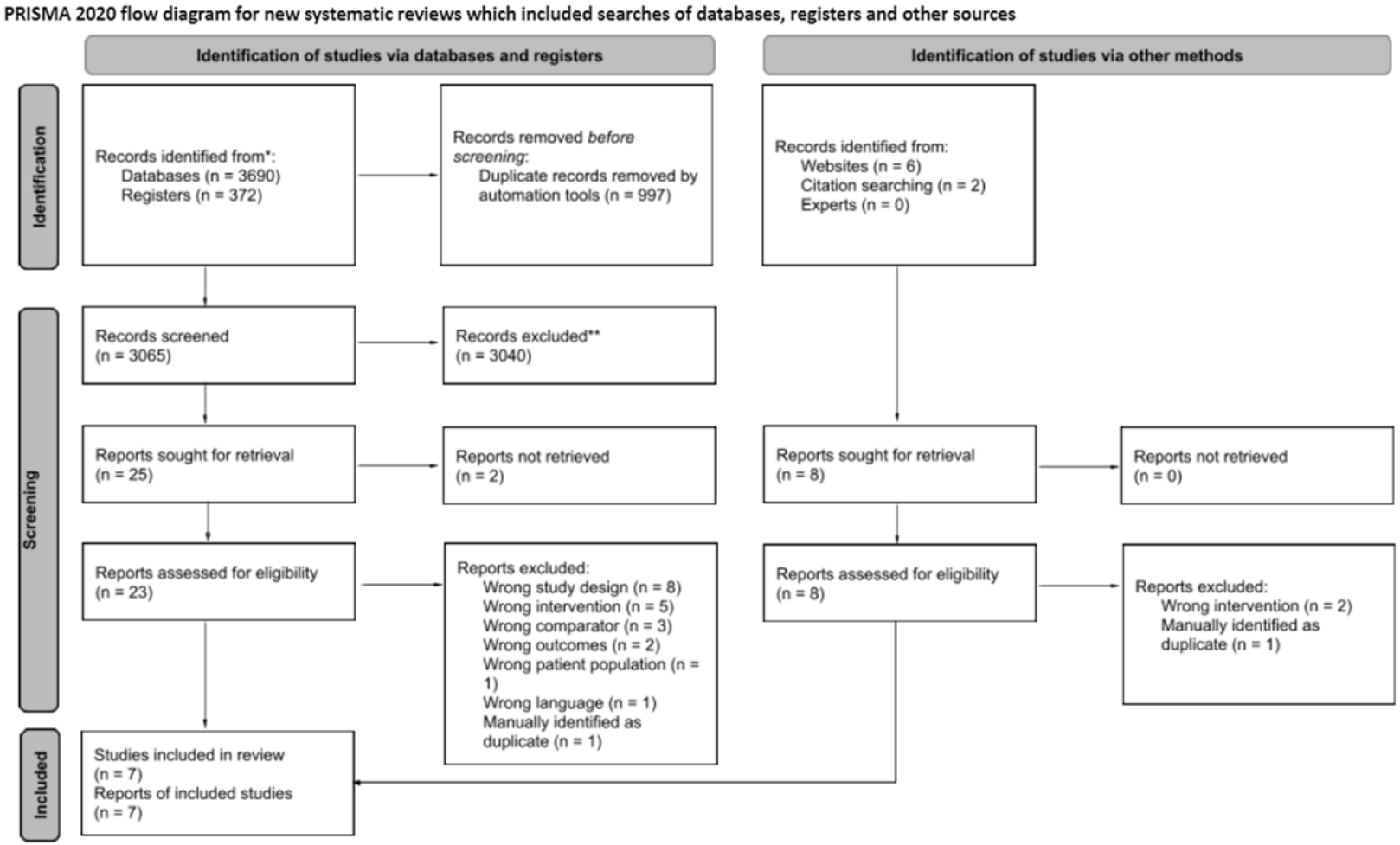

Table 5: Overdose Response - Study description and PICO elements of included sources

Citation	Study Type	Study Objective	Population/Problem	Intervention/Exposure	Comparator	Outcomes/Findings
Dezfulian, C., Orkin, A. M., Maron, B. A., Elmer, J., Girotra, S., Gladwin, M. T., Merchant, R. M., Panchal, A. R., Perman, S. M., Starks, M. A., van Diepen, S., Lavonas, E. J., & On behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Council on Clinical Cardiology. (2021). Opioid-Associated Out-of-Hospital Cardiac Arrest: Distinctive Clinical Features and Implications for Health Care and Public Responses: A Scientific Statement From the American Heart Association. Circulation, 143(16). https://doi.org/10.1161/CIR.0000000000000958	Guideline (Scientific Statement)	"This scientific statement aims to address this knowledge gap by defining unique features of OA-OHCA epidemiology, pathophysiology, and patient management that may require targeted guidelines. We also suggest that the distinct features of OA-OHCA demand a critical appraisal of education and policy decisions to improve outcomes." (p. e837)	People experiencing opioid-associated out-of-hospital cardiac arrest	Naloxone administration, overdose response, and post resuscitation care (discusses responses by the general public, health care professionals, and trained laypeople)	This source is not primary research, but discusses evidence on delivering compressions and rescue breathing/airway management	Mortality; and brain, cardiac, pulmonary vascular and other organ morbidity
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 (Question 1)	Guideline (Best Practice)	"Given the heterogeneity of suggested practices for opioid overdose response (providing breaths, providing compressions, providing both), this clinical guidance aims to produce a comprehensive guide based on best practices	People experiencing opioid overdose in the community	Cardiopulmonary resuscitation and naloxone administration by the general public in the community context	This source is not primary research, but discusses chest compressions and/or mouth-to-mouth ventilation in addition to naloxone.	Harms associated with overdose

		for responding to opioid overdoses with naloxone for the public, including people at risk of witnessing an overdose who may have limited training in cardiopulmonary resuscitation (CPR) and naloxone administration." (p. 2)				
Leece, P. (2016). Evidence Brief: Evidence on rescue breathing or chest compressions in local naloxone programs. Ontario Agency for Health Protection and Promotion (Public Health Ontario).	Grey Literature (Evidence Brief)	"we sought to review the quality of the HSFC/AHA guideline and other recent scientific guidelines on this topic that were based on systematic reviews. We also sought to review any new direct or indirect scientific evidence on effective responses to opioid-related emergencies since the AHA guideline was published that could be used for decision-making if an OEND program were considering an alternate algorithm compared to the HSFC/AHA guideline." (p. 2)	Adults experiencing opioid-associated out of hospital cardiac arrest	Resuscitation by adult laypersons	Rescue breathing only, conventional CPR, or neither with or without naloxone administration	Survival
Mitra, S., Schoffel, L., & Globerman, J. (2016). Chest compressions and rescue breathing when administering naloxone in opioid overdose. Ontario	Grey Literature (Rapid review and	To identify the best evidence "about the use of chest compressions and/or	People experiencing opioid overdoses	Overdose response with naloxone administration	Chest compressions only, rescue breathing only, chest compressions and	Not explicitly stated

HIV Treatment Network. https://www.ohtn.on.ca/wp-content/uploads//rapid-response/RR108_Opiod-Overdose.pdf	recommendations)	the use of rescue breathing when responding to an opioid overdose and administering naloxone". (p. 1)			rescue breathing together (CPR)	
New York State. (2016). Technical Working Group on Resuscitation Training in Naloxone Provision Programs: 2016 Report (p. 16). New York State, Department of Health, AIDS Institute. https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/docs/resuscitation_training.pdf	Grey Literature (report and guidance)	"The New York State Department of Health (NYSDOH) convened a Technical Working Group on Resuscitation Training in Naloxone Programs to ensure that overdose programs in New York State (NYS) and elsewhere are afforded the best possible resuscitation protocol guidance tailored to suspected opioid overdoses in diverse settings. The group discussed the relevant medical literature, current practices and available Health Department data and reached the following conclusions" "The goal of the Working Group was to ensure that overdose programs in NYS and elsewhere are given the best possible resuscitation protocol guidance tailored to suspected opioid overdoses in diverse	People experiencing an opioid overdose (sought to train potential witnesses to an opioid overdose in the processes of overdose recognition) (p 4)	Bystander provision of naloxone and training in Naloxone provision programs	Rescue breathing, chest compressions, chest compressions only in the context of sudden cardiac arrest, chest compression only in the context of respiratory arrest (p 4-5)	Not explicitly stated but discuss impact of community-based naloxone and mortality

		settings. The Working Group included individuals with a range of backgrounds in the areas of emergency medicine, prehospital services, primary care, addiction medicine, cardiology, government, and community naloxone programs. The immediate goal was to develop recommendations to inform opioid overdose training in NYS." (p.1, 3)				
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/ (Key question 4)	Guideline	"The objective of these guidelines is to reduce the mortality and morbidity of opioid overdose by improving the pre-hospital management of opioid overdose" (p. 4)	People experiencing opioid overdose Key question 1 also includes: "People likely to witness an opioid overdose" (p 22)	Standard CPR based on the "ABC" approach	Resuscitation based on chest compression only CPR (p 50)	Overdose mortality, overdose complications such as aspiration, overdose morbidity or prolonged adverse outcomes of opioid overdose, opioid withdrawal reaction to naloxone, adverse effects of resuscitation, and psychosocial interventions/referral to treatment post overdose

Seal, K. H. (2005). Naloxone Distribution and Cardiopulmonary Resuscitation Training for Injection Drug Users to Prevent Heroin Overdose Death: A Pilot Intervention Study. Journal of Urban Health: Bulletin of the New York Academy of Medicine, 82(2), 303–311. https://doi.org/10.1093/jurban/jti053	Pilot Study		People who use Injection drugs	Overdose prevention and management training	N/A	Safety and feasibility of training injection drug using partners to perform CPR and administer naloxone

Table 6: Overdose Response - Quality of evidence table for outcomes reported

Outcome(s)	# of studies and study design	Risk of bias based on PHO MetaQat	Inconsistency	Indirectness	Imprecision	Overall quality of evidence
No outcomes reported, but recommendations made	6 studies 3 clinical guidelines (Dezfulian et al., 2021; Jobin & Rossignol, 2018; WHO, 2014) 3 grey literature reports (Ontario HIV Treatment Network, 2016; Public Health Ontario & Leece, 2016; Technical Working Group on Resuscitation Training in Naloxone Programs, 2016)	**Low** **Rationale**: Most information is from studies at low risk of bias. **Impact on quality:** Not downgraded.	**Moderate** **Rationale**: Study recommendations vary. **Impact on quality:** Downgraded one level.	**High** **Rationale**: Recommendations are based largely on indirect evidence. **Impact on quality:** Downgraded one level.	**Not applicable** **Rationale**: Studies did not report outcomes. **Impact on quality**: Not downgraded.	Very low
Rates of survival	1 pilot and feasibility study (Seal et al., 2005)	**High** **Rationale**: Information is from a study at risk of bias (selection bias; reliance on self-reported data). **Impact on quality:** Downgraded one level.	**Not applicable** **Rationale:** Only one study identified. **Impact on quality:** Not downgraded.	**Moderate** **Rationale**: Study was not designed to assess survival rates. **Impact on quality:** Downgraded one level.	**High** **Rationale**: No estimate of effect; small total sample size . **Impact on quality**: Downgraded one level.	Very low

