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Comparative Effectiveness and Cost-effectiveness of Intranasal Naloxone Compared to Intramuscular Naloxone

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1 Abbreviations

ACCH	Alberta Community Council on HIV
AHS	Alberta Health Services
BC	British Columbia
CACS	Comprehensive Ambulatory Classification System
CASP	Critical Appraisal Skills Programme
CBN	community-based naloxone
CMG	Case Mix Grouper
CI	confidence interval
ED	emergency department
EMS	emergency medical services
FDA	Food & Drug Administration
GCS	Glasgow Coma Score
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IN	intranasal
IM	intramuscular
IQR	interquartile range
IV	intravenous
MD	mean difference
MFR	Medical First Response
N/A	not applicable
NHIB	Non-Insured Health Benefits
PROSPERO	International Prospective Register of Systematic Reviews
PSA	probabilistic sensitivity analyses
RCT	randomized controlled trial
ROBINS-I	Risk of Bias in Non-Randomized Studies of Interventions
RR	risk ratio
QALY	quality adjusted life-year
SD	standard deviation

WHO	World Health Organization

2 Executive Summary

This report presents the findings and conclusions of a provincial health technology assessment (HTA) on intranasal (IN) naloxone. The primary research objectives for this HTA were to determine:

1. The clinical effectiveness of IN naloxone compared to intramuscular (IM) and intravenous (IV) naloxone.
2. The ease of use and impact on the patients and care providers associated with IN naloxone.
3. The cost-effectiveness of IN naloxone formulations.
4. The budget impact of expanding availability of IN naloxone formulation in Alberta.

Background:

Opioid overdose occurs as a result of opioid misuse, such as consuming opioids in large quantities or in a manner that is not indicated (e.g., crushing an extended-release tablet instead of consuming it whole), leading to respiratory depression, unconsciousness, and death. In the first six months of 2020 in Alberta, there have been 2,105 suspected opioid-related overdoses and 449 apparent unintentional opioid-related deaths. Naloxone (naloxone hydrochloride) is an opioid-antagonist medication that can be used to rapidly block or reverse the effects of opioid overdose. Naloxone is available as an IN spray, an IM or subcutaneous injection, or intravenous infusion. Although injectable naloxone is rapid acting, it requires availability of sterile injection equipment and administration training, and, in Alberta, its administration by first responders is restricted to those covered by the Ministerial Order. Administration of IN naloxone is characterized by increased portability and ease of use by laypersons; however, nasal formulations are more expensive (range of $42 to $62.70 per dose for IN naloxone, with kits containing two doses, compared to the price of $12 for a dose of IM naloxone, with kits containing three doses). Currently, IN naloxone is only publicly funded in Ontario, Quebec, and the Northwest Territories, as well as for persons covered under the federally administered Non-Insured Health Benefits (NIHB) Program.

Methods:

The following methodological approaches were used to gather and synthesize the available evidence:

I. Systematic review of clinical effectiveness comparing IN naloxone to other formulations
II. Systematic review of patient and caregiver perspectives on the impact and ease of IN naloxone use
III. Cost-effectiveness analysis of IN naloxone compared to IM naloxone
IV. Interactive budget impact analysis tool

Key Findings:

The systematic review of clinical effectiveness identified seven studies: four randomized controlled trials (RCTs) and three non-RCTs. Given the limited data, RCT and non-RCT evidence was pooled for meta-analysis, and separate meta-analyses were conducted for IN naloxone versus IV or IM naloxone. The quality of the RCT evidence was generally judged to be of some concern for bias, whereas the quality of the non-RCT evidence was deemed to be of moderate risk of bias.

There are no statistically significant differences in most clinical outcomes between IN and non-IN naloxone. However, a meta-analysis of the evidence found that individuals receiving IN naloxone were significantly more likely to require supplemental naloxone (additional dose of naloxone due to lack of effectiveness of the initial dose), than those receiving it intramuscularly or intravenously (RR: 2.23, 95% CI: 1.70-2.91). IN naloxone was found to result in statistically significantly longer clinical response time (outcome measure not defined by the authors, MD: 1.12, 95% CI: 0.76-1.48) and lower post-naloxone respiratory rate than IV naloxone (MD: -1.50, 95% CI: -2.48— -0.52), but there were no differences between the two with respect to change in respiratory rate from baseline (MD: -1.54, 95% CI: -3.52-0.44). IN naloxone was not significantly different from IM naloxone with respect to time to respiratory response or adverse events (e.g., agitation, headache, nausea, and vomiting).

The systematic review identified eight studies: one was a qualitative study and seven studies reported on survey/quantitative data on patient (n=3) and provider perspectives (n=5). In the qualitative study examining patient experiences with IN and IM naloxone, most participants were reported to follow administration instructions for IN naloxone that they received during training, but some reported struggling to assemble their IN naloxone kit. It should be noted that the IN naloxone kit examined in this study was a multi-step atomizer spray which may not be reflective of the devices currently available on the Canadian market (e.g., NARCAN® single-step spray). Participants who deviated from the administration instructions cited reasons such as worry over the overdose victim was not regaining consciousness immediately, needing to confirm that the naloxone was effective ("to be on the safe side"), and large quantity of drugs consumed by the overdose victim. Across the survey/quantitative data studies, IN emerged as the preferential route of administration across both the patient and provider studies. Reasons for this preference included ease of administration, reduced blood-borne viruses risk, eliminating the need to carry needles/syringes, painlessness, vein preservation, and less alarming public use. Across the survey studies examining IN naloxone training for providers, IN naloxone was reported to be easy to use by almost all participants.

In the base case cost-effectiveness analysis examining IN and IM routes of naloxone, IN had a higher cost and equivalent or lower effectiveness than IM naloxone, and was therefore dominated (ICER: -$807.66/reversal; 95% CI: -$983.80 to -$683.42). The cost-effectiveness of IN compared to IM naloxone was sensitive to bystander and first responder willingness to administer. The lifetime time horizon scenario analysis found that IN naloxone is equivalent to IM naloxone. For both routes of administration, mean costs and QALYs were within the 2% margin of error introduced through probabilistic analysis.

The three budget impact analysis scenarios considered were: 1) status quo, 2) technology mix of IN and IM naloxone, and 3) extending expiration dates from 2 to 3 years. In all three budget impact analysis scenarios for naloxone for the treatment of opioid overdoses by bystanders and non-medical first responders, IN naloxone was associated with higher costs when compared to IM naloxone. In all scenarios considered, the estimated budget impact to the province to distribute naloxone kits over 3 years is approximately $19 million. Scenario one demonstrates

how costs to the province increase as the number of naloxone kits distributed increases. In scenario two, we see that as the proportion of IN kits distributed increases, the total costs for naloxone increases. Although these costs are not borne by Alberta Health, they would be paid for by the organizations that are delivering and using the naloxone. In the third scenario, impacts of extending the shelf life of naloxone kits are explored. This is estimated to increase the number of viable naloxone kits in circulation, at reduced cost to the province. An interactive budget impact analysis tool was developed that could be adapted to accommodate future data regarding naloxone kit distribution.

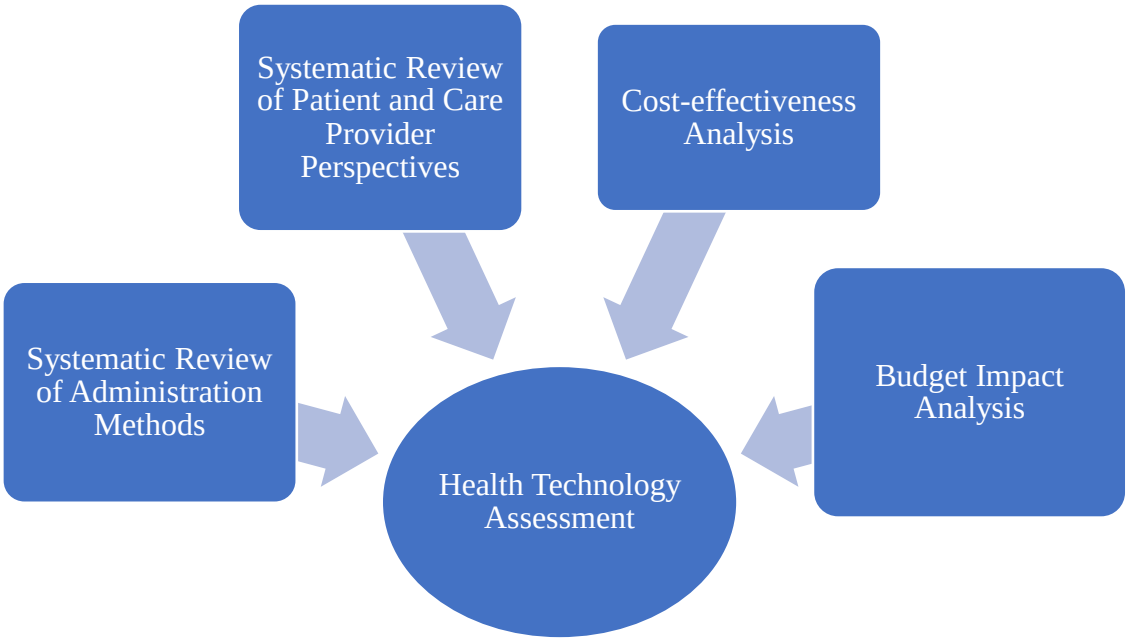
Conclusions:

Broadly, the evidence herein describes how IN and non-IN administration have benefits and drawbacks in terms of clinical effectiveness and safety, patient and caregiver preferences, cost-effectiveness, and estimated budget impact. A systematic review of clinical effectiveness found IN, and non-IN administration to be equivalent for clinical effectiveness and safety outcomes such as respiratory response, clinical response rate, and risk of adverse events. However, a statistically significant proportion of patients receiving IN naloxone appear to require supplemental naloxone when compared to those receiving naloxone intramuscularly or intravenously. Limited literature was found on patient and caregiver perspectives on naloxone administration method; included studies identified IN as the preferred route for administration. The cost-effectiveness model found IN to have a higher cost and equivalent or lower effectiveness, resulting in IN naloxone administration being dominated. Based on these findings, a budget impact analysis was developed to understand the predicted budget impact. In all three scenarios, IN naloxone was associated with higher costs when compared to IM naloxone. In all scenarios considered, the estimated budget impact to the province to distribute naloxone kits over 3 years is approximately $19 million.

3 Purpose of this Health Technology Assessment

The purpose of this health technology assessment (HTA) is to synthesize the evidence on intranasal (IN) naloxone. It synthesizes the available literature on clinical effectiveness of IN naloxone compared to other administration methods, summarizes the findings from a systematic review of patient and care provider perspectives, and presents a cost-effectiveness analysis. Finally, a budget impact analysis is presented with a range of implementation scenarios, each with unique advantages and disadvantages including impact on health and non-health benefits, provincial expenditure (Figure 1).

Figure 1. Summary of Process



4 Research Question and Objectives

The primary research objectives of this health technology assessment (HTA) were to determine:

1. The clinical effectiveness of intranasal (IN) naloxone compared to intramuscular (IM) or intravenous (IV) naloxone.
2. The ease of use and impact on the patients and care providers associated with IN naloxone.
3. The cost-effectiveness of IN naloxone formulations.
4. The budget impact of expanding availability of IN naloxone formulation in Alberta.

A variety of methodological approaches were used to gather and synthesize the available evidence in order to address the primary research question. The following methodologies were used:

I. Systematic review of clinical effectiveness comparing IN naloxone to other formulations
II. Systematic review of patient and provider perspectives on the impact and ease of IN naloxone use
III. Cost-effectiveness analysis of IN naloxone compared to IM naloxone
IV. Interactive budget impact analysis tool

5 Background

5.1 Overview of Opioid Overdose

5.1.1 Symptoms and Prevalence

Opioids are a class of analgesic drugs that are commonly used to manage pain.[1] Derived from either natural (e.g., poppy seed), semi-synthetic, or fully-synthetic compounds, opioid substances cause a euphoric effect when ingested, which leads them to be consumed for non-medical reasons.[1] Common naturally occurring opioid compounds include morphine and codeine; semi-synthetic opioid compounds include heroin and oxycodone; and fully-synthetic opioid compounds include fentanyl, tramadol, and methadone.[2] When ingested, opioid compounds bind to opioid receptors in the brain, thereby exerting their sedative or analgesic effect, but also leading to other effects, such as respiratory depression.[2] Opioid overdose occurs as a result of opioid misuse, such as consuming opioids in large quantities or in a manner that is not indicated (e.g., crushing an extended-release tablet instead of consuming it whole), leading to respiratory depression, unconsciousness, and death.[3]

In 2019, there were 21,203 suspected opioid-related overdoses across Canada, which resulted in 3,823 apparent opioid-related deaths.[4,5] Of these deaths, 94% were deemed to be accidental; 77% involved fentanyl or fentanyl analogues, and 72% involved one or more non-opioid substances (e.g., alcohol, cocaine, benzodiazepines).[4] Victims of accidental opioid overdoses were most often male (74%) and in the 30-39 year-old age range (28%). Data from completed investigations from six provinces suggests that, across all the accidental opioid-related deaths, 68% involved non-pharmaceutical opioids, 21% involved pharmaceutical opioids only, and 9% involved both.[4] Similar demographic characteristics were observed in Alberta in 2019, which recorded 3,536 suspected opioid-related overdoses and 639 apparent opioid-related deaths.[6] In the first six months of 2020 in Alberta, there have been 2,105 suspected opioid-related overdoses and 449 apparent unintentional opioid-related deaths.[7] A summary of suspected-opioid-related overdoses and apparent opioid-related deaths in Alberta and across Canada for the past five years (most recent data available) is provided in
Table 1.

Table 1. Numbers of Suspected Opioid-related Overdoses and Apparent Opioid-related Deaths in Alberta and across Canada, 2016-2020

	Alberta		Canada	
Year	**Suspected opioid-related overdoses[5,7]**	**Apparent opioid-related deaths[4,7]**	**Suspected opioid-related overdoses[5]**	**Apparent opioid-related deaths[4]**
2016	N/A	602	N/A	3,025
2017	2,643	744	16,548	4,147
2018	4,206	849	20,432	4,398
2019	3,536	639	21,203	3,823
2020*	2,105	449	N/A	N/A

*Data for January-June 2020
Abbreviations: N/A: not available

5.1.2 Risk Factors

Risk factors for opioid overdose tied to current use of opioids or other substances include:[1]

- having a pre-existing opioid use disorder
- injecting opioids
- resuming opioid use following an extended period of non-use (e.g., following detoxification or release from incarceration)
- using prescription opioids without medical supervision
- using a high prescribed dosage of opioids (>100 mg of morphine or equivalent daily)
- using opioids in combination with alcohol or substances that supress respiratory function (e.g., benzodiazepines)

Other risk factors for opioid overdose include demographics (e.g., male gender, middle age), socioeconomic factors (e.g., low socioeconomic status, unemployment), and concurrent mental health or medical conditions (e.g., heart failure, HIV, liver or lung disease).[1,8] Social or situational risk factors include using opioids alone or in an unfamiliar environment and using opioids from an unknown source or dealer.[9]

5.2 Naloxone

5.2.1 Overview

Naloxone (naloxone hydrochloride) is an opioid-antagonist medication that is used to rapidly block or reverse the effects of opioid intoxication.[3] When used on its own, naloxone provides a rapid and effective reversal of an opioid overdose. When used in combination with buprenorphine (Suboxone), naloxone is used as a maintenance treatment for opioid dependence. Although the exact mechanism of action of naloxone is not well-understood, evidence suggests that naloxone antagonizes the effects of opioids by competing for the same receptor sites, most notably the mu-opioid receptor.[10] Naloxone injection is part of the World Health Organization's (WHOs) Model List of Essential Medicines, which includes medicines considered to be the most necessary for meeting the needs of the health care system.[11] Naloxone has been available in Canada for 40 years, and take-home naloxone kits are available without prescription at most pharmacies.[12] In Alberta, community-based naloxone kits are distributed primarily from community pharmacies and community-based harm reduction programs.[6]

5.2.2 Administration Methods

Naloxone is available as an intranasal (IN) spray, intramuscular (IM) or subcutaneous injection, or intravenous (IV) infusion.[3] Appropriate dosage of naloxone depends on which formulation is used and the context in which it is administered. Injectable forms of naloxone can be administered intravenously, intramuscularly, or subcutaneously using a formulation containing 0.4 to 2 mg of naloxone; subsequent administrations of 0.4 mg of naloxone are recommended every two-to-three minutes until desired degree of reversal is reached.[13] IN naloxone administration involves using an atomizer connected to a syringe to spray a dose containing either 2 mg or 4 mg of naloxone into the patient's nostril; a second administration is recommended in the event that the patient does not respond after two-to-three minutes or responds but relapses into a respiratory depression.[14]

Currently, IN naloxone is only publicly funded in Ontario, Quebec, and the Northwest Territories, as well as for persons covered under the federally administered Non-Insured Health Benefits (NIHB) Program.[15,16] As a result, freely available take-home naloxone kits available in other jurisdictions consist of IM naloxone only. In Alberta, an IM take-home naloxone kit

contains the following items: three vials of naloxone injection (0.4 mg/mL each); syringes; needles; alcohol swabs; gloves; a breathing mask; and an instruction pamphlet on how to respond to an overdose (Figure 2).[17] IN naloxone kits are not publicly funded in Alberta; however, kits are available and contain the following items: two doses of IN naloxone spray (4 mg each); gloves; a breathing mask; and an instruction pamphlet on how to respond to an overdose (

Figure 3). In Alberta, the cost of IN naloxone has been noted to range from $42 to $62.70 per dose, with kits containing two doses, compared to the price of $12 for a dose of IM naloxone, with kits containing three doses. [18]

Figure 2. Intramuscular Naloxone Kit

Source: Fulcrum Publishing Society[19]

Figure 3. Intranasal Naloxone Kit

Source: Government of Ontario[20]

Different naloxone administration methods are characterized by specific potential benefits and drawbacks (

Figure 4).[21] IM naloxone has the most rapid onset of action and is frequently used in situations where intravenous access is not readily available, often by first responders and emergency department care providers. Although injectable naloxone is rapid-acting, it requires availability of sterile injection equipment and administration training. In Alberta, its administration by first responders is restricted to those covered by the Ministerial Order.[22] Administration of IN

naloxone is characterized by increased portability and ease of use by laypersons; however, nasal formulations have been noted to have poor bioavailability (i.e., degree to which the drug gets absorbed by the body) particularly with patients with any kind of nasal obstruction (e.g., nasal secretions, blood), and to be more expensive.[21,23] Lastly, as previously stated, a dose of IN naloxone has been reported to be several times more expensive than IM naloxone: range of $42 to $62.70 per dose for IN naloxone, with kits containing two doses, compared to the price of $12 for a dose of IM naloxone, with kits containing three doses.[18]

Figure 4. Potential Benefits and Drawbacks of Intramuscular versus Intranasal Naloxone

Intramuscular Naloxone	Intranasal Naloxone
• Rapid onset of action • Requires sterile injection equipment • Requires administration training • In Alberta, administration restricted to first responders covered by the Ministerial Order • Costs $12 per dose	• Noted to have poor bioavailability in patients with a nasal obstruction • Does not require sterile injection equipment, thereby increases portability and ease of use • Cost ranges from $42 to $62.70 per dose

6 Systematic Review of Clinical Effectiveness of Naloxone Administration Methods

Summary:

- Four RCTs were included, two with some concern for bias, one with high risk of bias and one with low risk of bias; three non-RCTs with moderate risk of bias were also included.
- There were no statistically significant differences in the time to respiratory response and adverse events between IN and IM naloxone.
- Individuals receiving IN naloxone had statistically significantly longer mean clinical response time (1.12 minutes longer) and statistically significantly slower mean post-naloxone respiratory rate (1.5/minute slower) compared with IV treatment, however the change in the respiratory rate from baseline was not statistically significant.
- Individuals receiving IN naloxone had 2.6- and 2-fold increased risk of supplemental naloxone treatment than those receiving it intramuscularly or intravenously, respectively.

6.1 Purpose

To synthesize the published literature on the clinical effectiveness of intranasal (IN) naloxone compared to other naloxone formulations or placebo.

6.2 Methods

6.2.1 Search Strategy

A systematic review was completed. The literature search was conducted by following the Cochrane best practices.[24] Embase, MEDLINE, Cochrane CENTRAL, Database of Abstracts of Reviews of Effect, Cochrane Database of Systematic Reviews, and CINAHL were searched for studies published from inception until August 11th, 2020. Terms aimed at capturing the technology of interest, including "naloxone" and "Narcan" were combined with administration terms, such as "intranasal," "intravenous," and "intramuscular" using the Boolean Operator "and." Terms were searched as text words in titles and abstracts and as MeSH subject headings when applicable. The search was limited to English or French language studies, and a filter was used to exclude commentaries, editorials, and conference proceedings. The search strategy was developed by a research librarian and peer review of electronic search strategies (PRESS) was conducted by another research librarian.[25] The full search strategy is available in Appendix A. The reference lists of included studies were hand-searched to ensure all relevant literature was captured. A search of the grey literature was not conducted. This systematic review is registered

in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020203632.

6.2.2 Study Selection

Abstracts were screened in duplicate by two independent reviewers. Abstracts proceeded to full-text review if they: compared administration of IN naloxone (any) with another naloxone formulation or placebo; were a comparative study design; and reported on outcomes including, but not limited to time to adequate response, change in level of consciousness, vital signs, and arterial blood oxygen saturation. Citations were excluded if they failed to meet the inclusion criteria above, or if they: were editorials, case reports, or commentaries; or were published in languages other than English or French (
Table 2). Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review. Full-text review was completed in duplicate by two independent reviewers. Any discrepancies between reviewers were resolved through discussion and consensus. If required, a third reviewer was consulted.

Table 2. Inclusion and Exclusion Criteria for Systematic Review of Administration Methods

Inclusion Criteria	Exclusion Criteria

• Subjects with opioid overdose
• Intervention group receiving nasal naloxone.
• Comparator group receiving another naloxone formulation or placebo
• Clinical outcomes may include but are not limited to:
  ○ Time to adequate response
  ○ Change in level of consciousness
  ○ Vital signs
  ○ Arterial blood oxygen saturation
• Comparative study design
	• Editorials, case reports, commentaries
	• Studies published in languages other than English or French

6.2.3 Data Extraction

For all included studies, year of publication, country, study design, drug dose, administration methods, patient characteristics, and all outcomes reported were extracted in duplicate using standardized data extraction forms. Discrepancies between reviewers during data extraction were resolved through consensus.

6.2.4 Quality Assessment

The quality of randomized controlled trials (RCTs) was assessed using the Cochrane Handbook Risk of Bias Assessment Tool (version 5.1.0),[26] while the non-randomized studies were assessed with the Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[27] Each RCT was assessed using five criteria broadly covering the areas of randomization, deviation from intended intervention, missing outcome data, measurement of outcome and selection of reporting result. Each criterion was assigned a rating of "low," "some," or "high" concern. The non-RCTs were assessed based on the following parameters: bias due to confounding, selection bias, bias in classification, bias due to deviations from intended interventions, bias due to missing data, bias in measurement and reporting bias. Each criterion was also assigned a rating of "low," "moderate" or "serious" risk of bias. Quality assessment was completed in duplicate and discrepancies were resolved through discussion. Studies were not excluded based on quality assessment.

6.2.5 Data Analysis

Meta-analyses were conducted to compare IN naloxone with IM and/or IV naloxone. Risk ratios (RRs) were estimated for the categorical outcomes, such as adverse events and the proportion of participants requiring supplemental or rescue naloxone. Mean differences (MDs) were estimated for continuous outcomes such as: respiratory response time, respiratory rate and change in respiratory rate.

Random-effects meta-analysis was conducted, utilizing the DerSimonian and Laird estimator for Tau.[28] Statistical heterogeneity was assessed using the I^2 measure, with values above or below 50% considered high and low heterogeneity respectively. A continuity correction of 0.5 was used

where appropriate, allowing the inclusion of zero-total event trials.[29] All analyses were completed in R version 3.5.2.

6.3 Findings

6.3.1 Study Characteristics

The search strategy yielded 1115 unique citations, 1068 of which were excluded after abstract review. Forty-seven studies proceeded to full-text review. Forty studies were excluded for the following reasons: outcomes not of interest (n=18), not a comparative study (n=9), study design not of interest (n=8), not an English or French study (n=1), non-human study (n=1), not the population of interest (n=1), article not retrievable (n=1), and duplicate study (n=1). A total of seven relevant studies were included in the final dataset (
Figure 5).[30-36]

The seven included studies included a total of 915 patients. Four studies compared IN with IV naloxone,[31-34] while three compared IN with IM naloxone.[30,35,36] Four of the studies were RCTs,[30,34-36] two were retrospective comparative cohort studies[32,33] and one was a non-randomized controlled study.[31] Three studies were conducted in Australia[30,35,36] and two studies each in Iran[31,34] and the USA[32,33] (Table 3).

Figure 5. PRISMA Flow Chart of Included and Excluded Studies

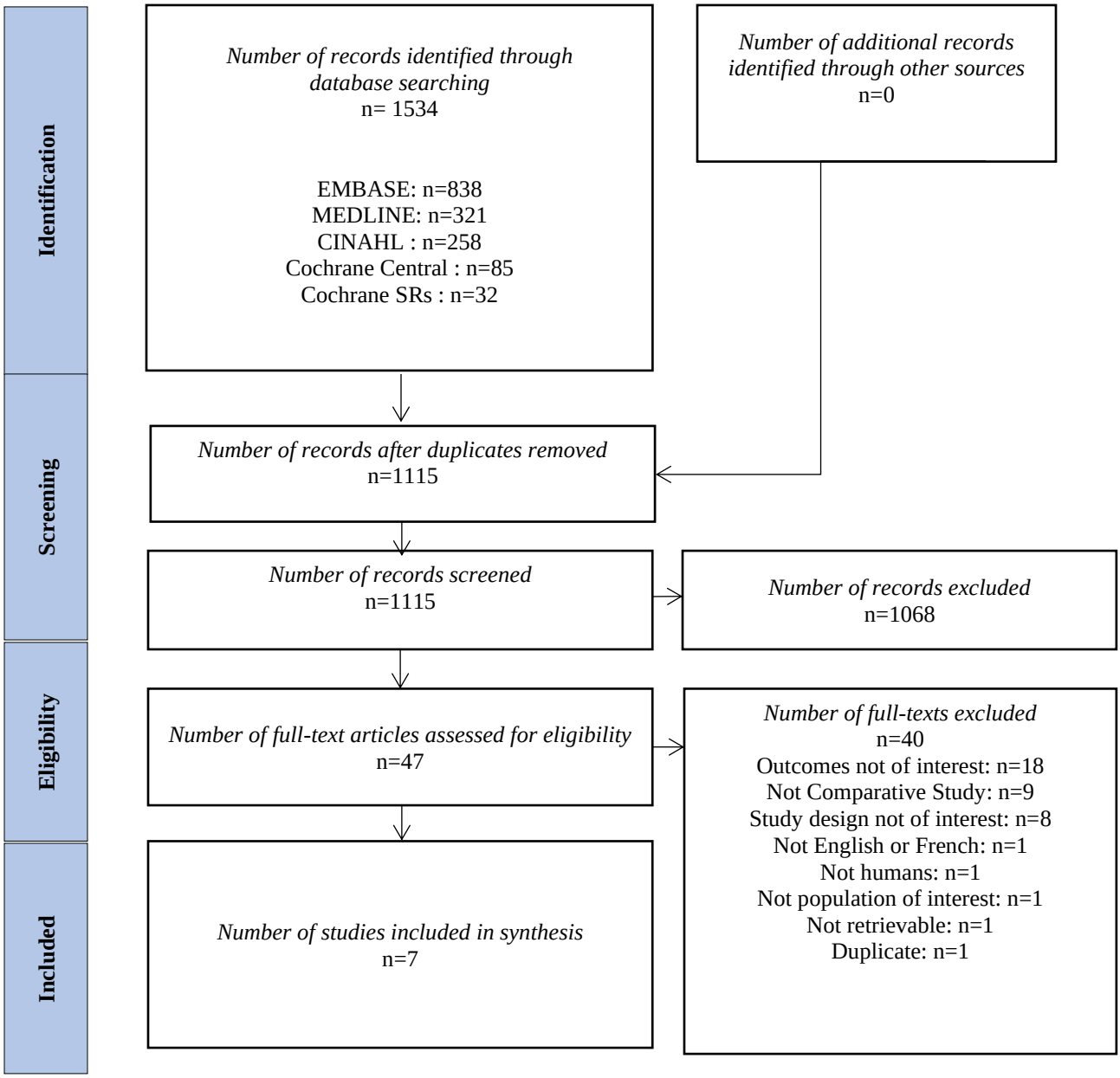


Table 3. Table of Study Characteristics

					Outcomes								
	Author/Design	**Characteristics**	**Inclusion and Exclusion**	**Intervention**	**Time to response**	**Adverse events**	**Rescue Naloxone**	**Respiratory Changes**	**GCS Changes**	**Oxygen saturation changes**	**Clinical Response Timee**	**Target GCS**	**BP Changes**
RCTs	Dietze, 2019[30] Australia Single centre	Age Range: 19-56 years Percent Female: 12.2% Total Sample Size:197	**Inclusion criteria:** All consenting clients with symptoms opioid overdose that required naloxone. Clinical criteria for overdose included reduced level of consciousness as measured by the Glasgow Coma Scale <13, Respiratory depression (RR<10), O2 saturation <95%. **Exclusion Criteria:** Not Reported	**Intranasal:** Sample size: 104 Dose: 800mcg Mean Age (SD): 34.4 (8.1) years **Intramuscular:** Sample size: 93 Dose: 800mcg Mean Age (SD): 33.6 (7.5) years	X	X	X						X
	Kelly, 2005[35] Australia Multicentre	Age Range: 13-57 years Percent Female: 28.4% Total Sample Size: 155	**Inclusion criteria:** Suspected opiate overdose with fewer than 10 respirations per minute and were not rousable **Exclusion criteria:** Not Reported	**Intranasal:** Sample size: 84 Dose: 2mg Median (Range): 28 (13-52) years **Intramuscular:** Sample size: 71 Dose: 2mg Median (Range): 30 (16-57) years	X	X	X					X	
	Kerr, 2009[36] Australia Multicentre	Age Range: Not Reported Percent Female: 36.5% Total Sample Size: 172	**Inclusion criteria:** Suspected opiate overdose [altered conscious state, pinpoint pupils, respiratory depression (respirations < 10)], unrousable as defined by Glasgow Coma Score (GCS) 12 and had no major facial trauma, blocked nasal passages or epistaxis **Exclusion criteria:** Potential participants who were treated by paramedics who had not been trained	**Intranasal:** Sample size: 83 Dose: 2mg Mean: 20.6 years **Intramuscular:** Sample size: 89 Dose: 2mg Mean: 31.8 years	X	X		X					
	Sabzghabaee, 2014[34] Iran	Age Range: 15-50 Percent Female: 24%	**Inclusion criteria:** Age 15-50, Suspected opioid overdose, clinical manifestation include myosis,	**Intranasal:** Sample size: 50 Dose: 0.4mg Mean Age (SD): 29.9 (8.4) years					X	X	X		X

	Single centre	Total Sample Size: 100	loss of consciousness. **Exclusion criteria:** Failing to respond to 0.4mg naloxone with increased level of consciousness or reversal of respiratory depression	**Intravenous:** Sample size: 50 Dose: 0.4mg Mean Age (SD): 33.2 (21.1) years									
Non-RCTs	Farnaghi, 2020[31] Iran Non-randomized controlled study	Age Range: 1-13 years Percent Female: 36.3% Total Sample Size: 44	**Inclusion criteria:** Opioid poisoning, 1-13 years old, no severe symptoms, paternal agreement. **Exclusion criteria:** Nasal congestion, severe poisoning and co-ingestion	**Intranasal:** Sample size: 22 Dose: 0.01mg/kg Mean Age (SD): 36.8 (19.7) months **Intravenous:** Sample size: 22 Dose: 0.01mg/kg Mean Age (SD): 38.2 (28.8) months			X	X	X	X	X		
	Merlin, 2010[32] USA Retrospective Comparative Cohort	Age Range: Not Reported Percent Female: 26% Total Sample Size: 93	**Inclusion criteria**: Illegal or nontherapeutic opioid use, evidence of opioid use observed by paramedics or positive urine toxicologic screen for opioids. **Exclusion criteria:** Cardiac arrest, intubation before naloxone administration, sedation by paramedics before naloxone administration, patients with end point data missing from patient care reports (PCRs).	**Intranasal:** Sample size: 38 Dose: 2mg Median Age (IQR): 36 (27-54) years **Intravenous:** Sample size: 55 Dose: 0.4-2mg Median Age (IQR): 42 (31-47) years			X	X	X				
	Robertson, 2009[33] USA Retrospective Comparative Cohort	Age Range: Not Reported Percent Female: 34.5% Total Sample Size: 154	**Inclusion criteria:** Treated with naloxone for suspected narcotic overdose (clinically suspected, RR 8/min or less) **Exclusion criteria:** Failure to be treated with naloxone, altered mental state not thought to be secondary to opioid overdose	**Intranasal:** Sample size: 50 Dose: 2mg Median Age (Range): 41 (18-72) years **Intravenous:** Sample size: 104 Dose: 1mg Median Age (Range): 44 (3-96) years			X	X	X				

Abbreviations: GCS: Glasgow Coma Score, IQR: interquartile range, RR: respiratory rate, SD: standard deviation, USA: United States of America

6.3.2 Quality Assessment

Four RCTs were assessed. Two studies were of low risk of bias regarding the randomization process,[30,35] while the remaining two had some concerns.[34,36] One study had some concern regarding deviations from intended interventions and measurement of outcomes,[34] while the remaining three studies were of low concern. All but one study[35] were of low risk for missing outcome. One study had a low risk of selection bias,[30] another was of high risk,[35] and two were of some concern.[34,36] The overall risk of bias was judged to be low in one study,[30] high in another[35] and of some concern in two studies[34,36] (Table 4).

Table 4. Risk of Bias Assessment for RCTs

Author (year)	Randomization process	Deviation from intended interventions	Missing Data Outcome	Measurement of Outcome	Selection of reported result	Overall Bias
Dietze, 2019[30]	Low	Low	Low	Low	Low	Low
Kelly, 2005[35]	Low	Low	High	Low	High	High
Kerr, 2009[36]	Some concerns	Low	Low	Low	Some concerns	Some concerns
Sabzghabaee, 2014[34]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns

Three non-RCT studies were assessed using the ROBINS-I tool. Two of the studies had serious risk of bias due to confounding,[32,33] while the third study was of a low risk.[31] All the three studies were of low risk of bias due to: the selection of participants into the study, classification of interventions, deviation from intended interventions, missing data and the selection of the reported results. Furthermore, all the three studies had a moderate risk of bias in the measurement of outcomes. All the three studies had moderate overall risk of bias (Table 5).

Table 5. Risk of Bias Assessment for Non-RCTs

Author (Year)	Confounding	Selection of participants	Classification of Interventions	Deviation from Interventions	Missing Data	Measurement of Outcomes	Selection of reported results	Overall Bias
Farnaghi, 2020[31]	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Merlin, 2010[32]	Serious	Low	Low	Low	Low	Moderate	Low	Moderate
Robertson,2009[33]	Serious	Low	Low	Low	Low	Moderate	Low	Moderate

6.3.3 Meta-analyses

6.3.3.1 IN versus non-IN Naloxone

A meta-analysis of six studies showed that individuals receiving IN naloxone were statistically significantly more likely to require supplemental naloxone than those receiving non-IN naloxone (RR: 2.23, 95% CI: 1.70-2.91) (

Figure 6). The difference in the clinical response rate was not statistically significant between IN naloxone and non-IN treatment (RR: 1.03,95% CI:0.82- 1.29) (Figure 7).

6.3.3.2 IN versus IM Naloxone

All of the studies evaluating supplemental naloxone treatment, time to respiratory response and adverse events following IN and IM naloxone were RCTs. Meta-analysis showed a statistically significant increase in supplemental naloxone use following IN compared with IM treatment (RR: 2.59, 95% CI: 1.63-4.12) (

Figure 6). The difference in the time to respiratory response was not statistically significant between IN and IM naloxone (MD: 5.12, 95% CI: -1.70-11.93)(Figure 8). The risks of adverse events, including agitation, headache, nausea and vomiting, were not statistically significantly different between IN and IM naloxone (Figure 9).

6.3.3.3 IN versus IV Naloxone

All the studies that evaluated supplemental naloxone use following IN and IV treatment were non-RCTs. There was a statistically significant increase in supplemental naloxone use following IN naloxone compared with IV treatment (RR: 2.06, 95% CI: 1.49-2.86) (

Figure 6

Figure 6. Supplemental or Rescue Naloxone Requirement with IN or Non-nasal Comparators

). Two studies, one RCT and a non-RCT, reported sufficient data for the meta-analysis of the post-naloxone respiratory rate, which was statistically significantly lower with IN than IV treatment (MD: -1.50, 95% CI: -2.48-0.52). Of the three studies with data on the change in the respiratory rate from baseline, two were non-RCTs. Meta-analysis of the three studies showed that the change in the respiratory rate from baseline was not statistically significantly different

between IN and IV naloxone (MD: -1.54, 95% CI: -3.52-0.44) (Figure 8), subgroup analysis of only the non-RCTs did not show any statistically significant difference between the two interventions (MD: -0.79, 95% CI:-3.19-1.61)(Figure 8). Analysis of two studies, a RCT and non-RCT showed that patients receiving IN naloxone had statistically significantly longer clinical response time (measure not defined by authors) than IV treatment (MD: 1.12, 95% CI: 0.76-1.48) (Figure 10).

6.3.3.4 Single Studies

Four studies reported the significance level for the clinical outcomes that could not be pooled for meta-analysis. These studies reported no statistically significant differences in the change in oxygen saturation[31] and the Glasgow Coma Scale[31,32] between IN and IV naloxone. The time to recovery from coma was also not statistically significantly different between IN and IM naloxone.[30,35]

Figure 6. Supplemental or Rescue Naloxone Requirement with IN or Non-nasal Comparators

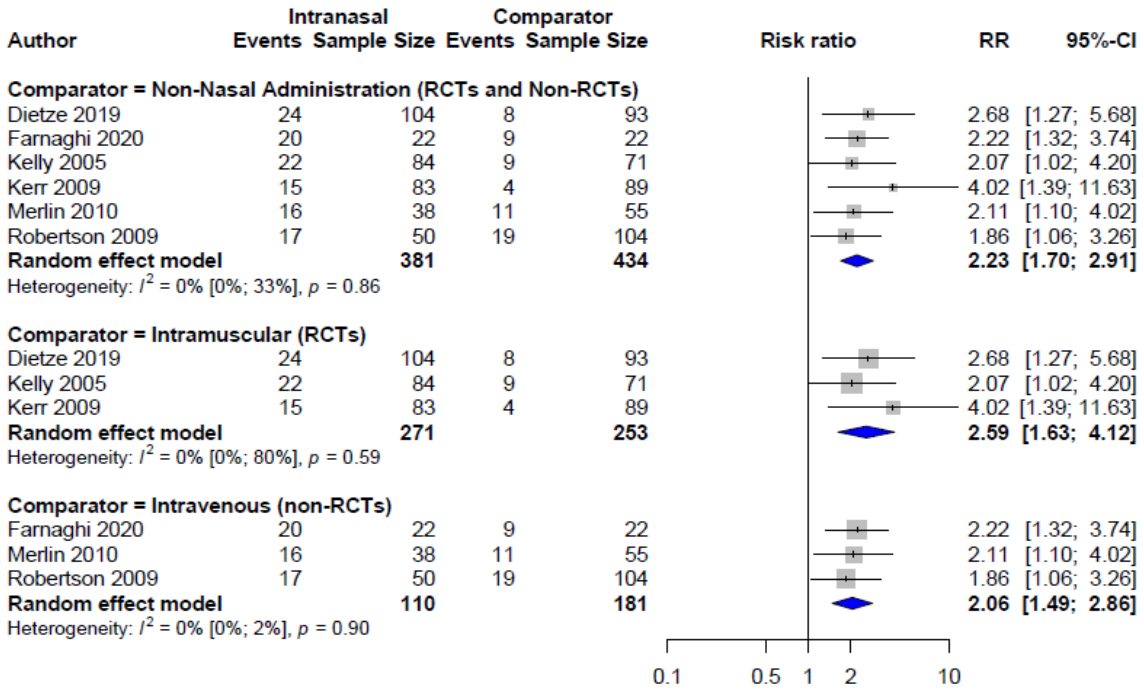


Figure 7. Clinical Response Rate with IN and non-IN Naloxone

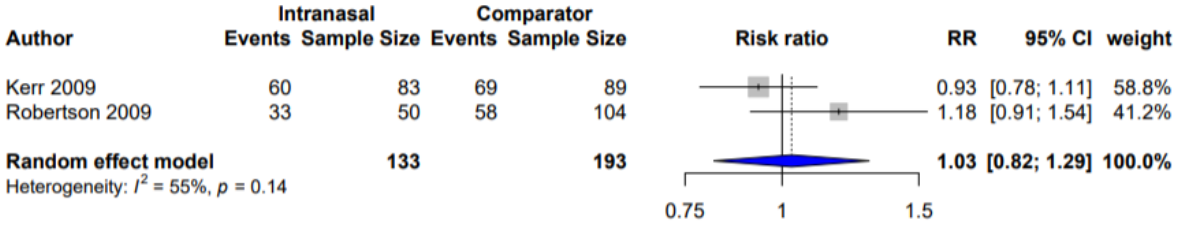


Figure 8. Respiratory Response with IN Naloxone and Non-nasal Comparators

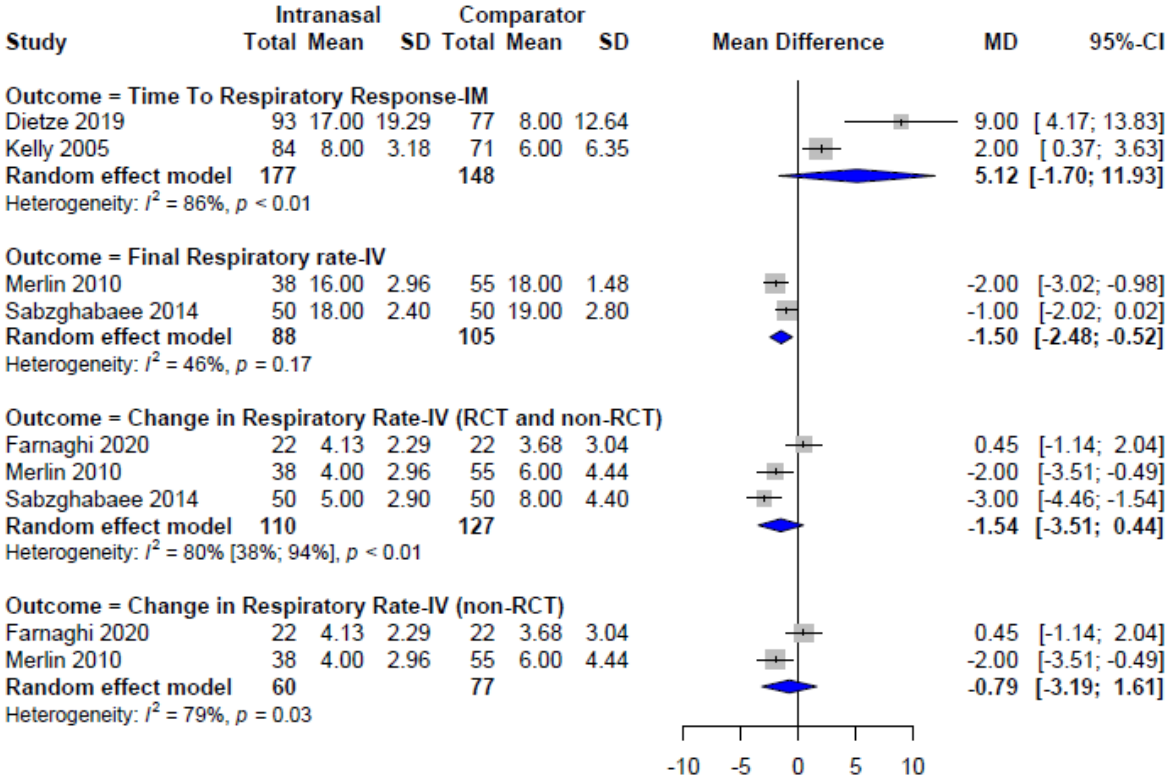


Figure 9. Adverse Events with IN and IM Naloxone

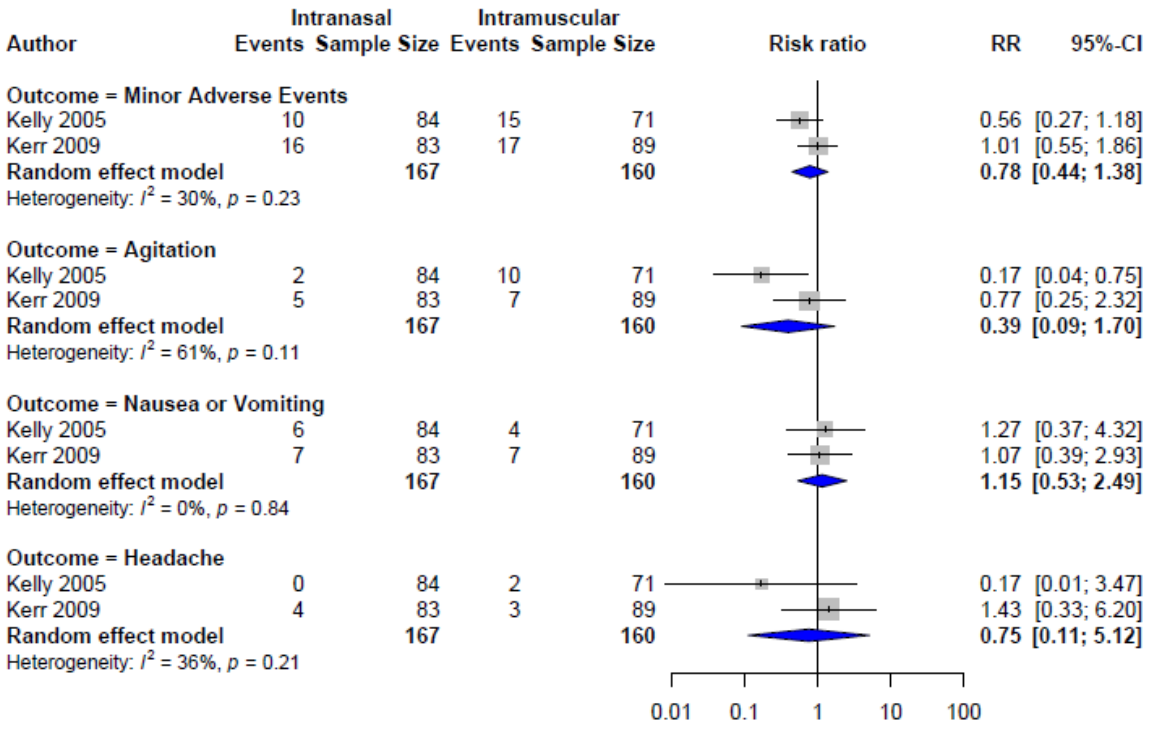
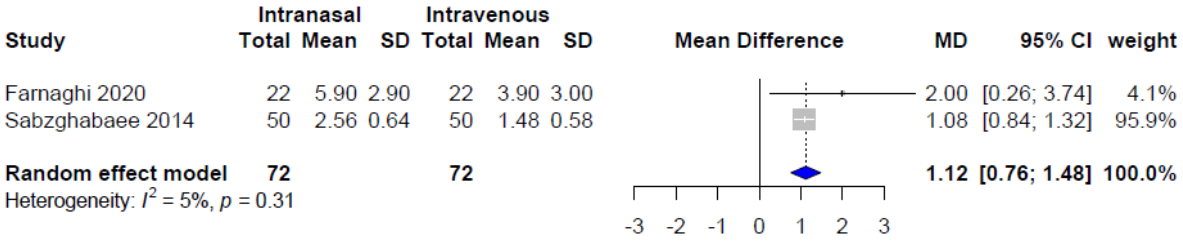


Figure 10. Clinical Response Time between IN and IV Naloxone



6.4 Conclusions

This systematic review found no statistically significant differences in most clinical outcomes between IN and non-IN naloxone. However, the clinical response time appears to be statistically significantly longer with IN compared with IV naloxone. A statistically significant proportion of patients receiving IN naloxone appear to require supplemental naloxone when compared to those receiving naloxone intramuscularly or intravenously. The safety profile of IN naloxone appears

to be comparable to IM naloxone. Several outcomes were not meta-analyzed due to insufficient data. These findings should be interpreted with caution because of the limited number of studies synthesized for each outcome.

7 Systematic Review of Patient and Care Provider Perspectives

Summary

- Eight studies were included in this systematic review of patient and care provider perspectives on IN naloxone administration: one was a qualitative study and seven studies reported on survey/quantitative data on patient (n=3) and provider perspectives (n=5).
- In the qualitative study examining patient experiences with IN and IM naloxone, most participants were reported to follow administration instructions for IN naloxone that they received during training, but some reported struggling to assemble their IN naloxone kit. Participants who deviated from the administration instructions cited reasons such as worry over the overdose victim was not regaining consciousness immediately, needing to confirm that the naloxone was effective ("to be on the safe side"), and large quantity of drugs consumed by the overdose victim.
- Across the survey/quantitative data studies, IN emerged as the preferential route of administration across both the patient and provider studies that examined it in comparison to other delivery routes. Reasons for this preference provided by patients included ease of administration, reduced blood-borne viruses risk, eliminating the need to carry needles/syringes, painlessness, vein preservation, and less alarming public use.
- Across the survey studies examining IN naloxone training for providers, IN naloxone was reported to be easy to use by almost all participants.

7.1 Purpose

To understand patient and care provider experiences with providing or receiving intranasal (IN) naloxone as reported in the published literature.

7.2 Methods

7.2.1 Search Strategy

A systematic review was completed. The literature search was conducted by broadly following the Cochrane methodology.[24,37] Embase, CINAHL, MEDLINE, PsycINFO, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews were searched for studies published from inception until August 11, 2020. Terms aimed at capturing the technology of interest, including "naloxone" and "Narcan" were combined with administration terms, such as "nasal", "intravenous", and "intramuscular" using the Boolean Operator "and." Terms were searched as text words in titles and abstracts and as MeSH subject headings when applicable. The search was limited to English or French language studies, and a filter was used to exclude commentaries, editorials, and conference proceedings. The search strategy was developed by a research librarian. The full search strategy is available in Appendix B. The reference lists of included

studies were hand-searched to ensure all relevant literature was captured. A search of the grey literature was not conducted. This systematic review is registered in the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42020203835.

7.2.2 Study Selection

Abstracts were screened in duplicate by two independent reviewers. Abstracts proceeded to full-text review if they consisted of literature assessing patient and care provider perspectives related to IN naloxone administration. Citations were excluded if they failed to meet the inclusion criteria above or if they were published in a language other than English or French (Table 6). Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review. Full-text review was completed in duplicate by two independent reviewers. Any discrepancies between reviewers were resolved through discussion and consensus. If required, a third reviewer was consulted.

Table 6. Inclusion and Exclusion Criteria for Systematic Review of Patient and Care Provider Perspectives

Inclusion Criteria	Exclusion Criteria
• Any study design assessing patient and care provider perspectives on intranasal naloxone administration.	• Studies not assessing patient and care provider perspectives on intranasal naloxone administration. • Studies published in languages other than English or French

7.2.3 Data Extraction and Analysis

Data were originally planned to be analyzed using the 'best-fit' framework synthesis methodology.[38,39] However, given the low number of qualitative studies identified in the review, data were synthesized narratively. Findings were synthesized by one reviewer and verified by another.

7.2.4 Quality Assessment

Quality assessment was not conducted because the range of study designs included in this systematic review precluded meaningful comparative quality assessment.

7.3 Results

7.3.1 Study Characteristics

A total of 1,942 citations were identified from the literature search, as follows: EMBASE (n=1,231), MEDLINE (n=620), CINAHL (n=414), PsychINFO (n=265), Cochrane CENTRAL Register (n=134), and the Cochrane Database of Systematic Reviews (n=58). After duplicates were removed, 1,942 unique abstracts were reviewed. Of these, 1,927 were excluded, and 15 studies were assessed for eligibility in full-text. Seven publications were excluded at full-text review because they did not report on nasal naloxone administration (n=5) or did not report on patient or care provider perspectives (n=2). Eight studies were included in the final narrative synthesis: one qualitative study[40] and seven studies reporting survey/quantitative data[41-47] (Figure 11).

The list of studies excluded at the full-text stage and reasons for exclusion are reported in Appendix B.

Five studies were from the USA,[40,42,44,46,47] two from Ireland,[41,45] and one from Australia.[43] Most were published within the last five years. Five studies examined perspectives of providers on IN naloxone, including general practitioners (GPs),[41] mixture of providers (e.g., physicians, physician assistants),44 advanced paramedic trainees,[45] first-year student pharmacists,[47] and police officers.[46] Four studies examined perspectives of patients, including persons taking a prescribed opioid for pain,[42] people who inject drugs,[43] patients receiving treatment for drug and/or alcohol detoxification,44 and persons with a recent history of heroin use.[40] Aside from one study,[42] studies generally included predominantly male participants. A narrative synthesis of the findings is reported below, with the summary of each individual study reported in Table 7.

Figure 11. PRISMA Flow Chart of Included and Excluded Studies

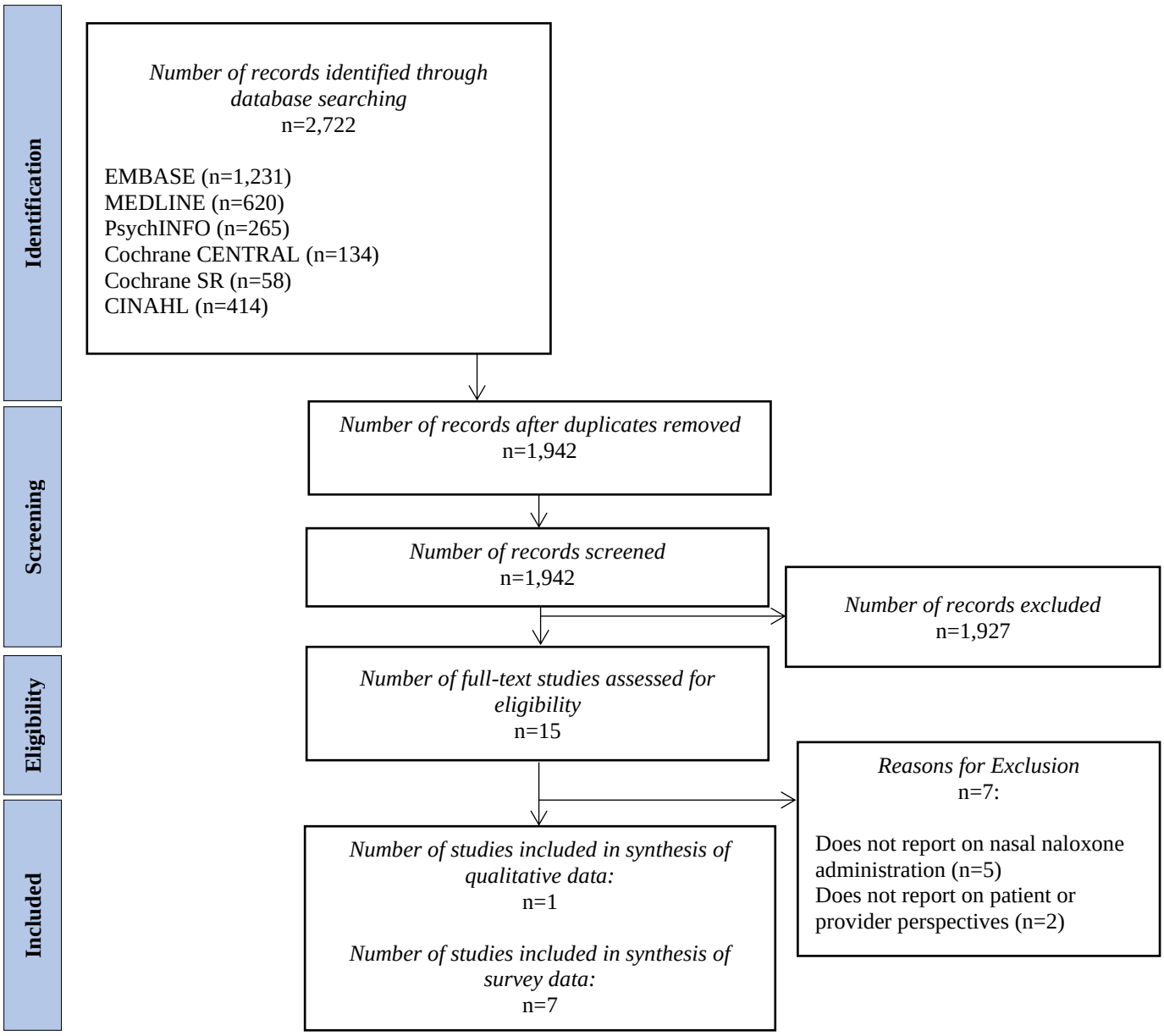


Table 7. Characteristics and Findings from Studies Included in the Systematic Review of Patient and Care Provider Perspectives

Author (Year), Country	Study Design	Population	Sample Characteristics	Findings Regarding IN Naloxone
Barry (2017), Ireland[41]	Paper-based, anonymous postal survey	GPs (N=448)	Males: 64.8% Age (years): ≤40 (15.3%), 41-50 (23.4%), >50 (61.3%) Work setting: rural (29.1%), urban (38.2%), mixed (32.7%) Practice provides care for patients who use illicit opiates: 75.3% Used naloxone for OD: 34.8% Patient of practice had OD: 34.4%	• IN naloxone was the preferred route for lay delivery of naloxone (mean rank = 1.34), when ranked from first to fourth preference, and most GPs who responded (81.7%, 331/405) reported it as their first preference.
Dunn (2018), USA[42]	Cohort survey study through Amazon MTurk	Cohort 1: Persons taking a prescribed opioid for pain (N=501) Cohort 2: Persons taking a prescribed opioid for pain, experiencing pain for ≥3 months (N=172)	<u>Cohort 1:</u> Males: 44.7% Age (years): 18-25 (13%), 26-35 (39.7%), 36-45 (13.7%), 46-55 (11.9%), ≥56 (6%) Duration of opioid prescription (years): ≤1 (57.1%), 1-4 (29.9%), ≥5 (13%) <u>Cohort 2:</u> Males: 44% Age (years): 18-25 (25.6%), 26-35 (42.9%), 36-45 (24.2%), 46-55 (11.8%), ≥56 (7.3%) Duration of opioid prescription:	• Respondents stated they were more willing to administer noninjectable formulations of naloxone (IN, sublingual, buccal) over injectable formulations. • Both cohorts ranked the noninjectable formulations (IN, sublingual, and buccal) as more preferable than the injectable formulations. • Respondents in both cohorts indicated IN naloxone (44.9%) as the preferred route of administration. • None of the demographic or drug use characteristics examined were significantly associated with preference for injectable versus noninjectable formulations.

Author (Year), Country	Study Design	Population	Sample Characteristics	Findings Regarding IN Naloxone
			≤1 year (67.3%), 1-4 years (22.6%), ≥5 years (10.1%)	
Kerr (2008), Australia[43]	Face-to-face interviews with a structured questionnaire	People who inject drugs (N=99)	Males: 72% Age (years): median=35 (range: 8 to 49) Duration of injecting heroin use (years): median=13 (range: 4 months to 31 years)	• Of those who regarded peer naloxone distribution favorably, IN administration was preferred (74%; 70/95). • Reasons given for IN preference included ease of administration, reduced blood-borne viruses risk, eliminating the need for needles/syringes on the person, vein preservation, painlessness, and less alarming public use. • No variable (e.g., age, gender, injection behaviour, duration of heroin use) was significantly associated with preference for administration of naloxone via the IN route.
Kirane (2016), USA[44]	Cross-sectional, interviewer-administered surveys; with a subset of self-administered surveys	Patients receiving treatment for drug and/or alcohol detoxification, (N=100) Providers (N=101)	<u>Patients:</u> Age (years): M=37.3 Males: 77% Past OD experience: 38% (7% of those in the past 3 months) Witnessed IN naloxone in use: 21% Know anyone who has used IN naloxone: 12% Providers: Level of training: physicians (61%), physician assistants (8%), registered nurses (8%), other (24%)	<u>Patients:</u> • 65% knew what IN naloxone is used for; however, 79% did not know how long IN naloxone lasts for; and 67% did not know where to access IN naloxone kits. • 99% felt that if a health care provider distributes IN naloxone, they would feel willing to be more open with that provider. • 58% felt that having IN naloxone may change their behaviours regarding opioid use, with 48% of those stating they would increase their use. • Knowledge of IN naloxone's clinical action, duration of action, legality of prosecution, and witnessing naloxone use in the past were not significantly related

Author (Year), Country	Study Design	Population	Sample Characteristics	Findings Regarding IN Naloxone
				to patients reporting IN naloxone access would increase their pattern of use. <u>Providers</u> • 24% reported completion of an IN naloxone-training course; 20% felt they knew where to refer patients for IN naloxone kits. • 96% accurately stated IN naloxone's purpose to treat overdose from any type of opiate or opioid, but only 41% were able to correctly identify the duration of action of IN naloxone to be up to sixty minutes. • 48% felt that providing IN naloxone kits would decrease the likelihood of a future OD event occurring, and 47% felt that it would decrease riskier use patterns.
McDermott (2012), Ireland[45]	RCT	Advanced paramedic trainees (N=18)	Males: N=15 Age (years): M=50.5 (range: 32 to 57)	• 89% (8/9) of trainees from the IN naloxone group "strongly agreed" that the IN technique was both easy to use and safe to use, compared to 5/9 trainees in the IV naloxone group reporting that it was easy to use and most (67%) saying that they "disagreed" that it was safe to use.
Neale (2019), USA[40]	Qualitative study	Persons with a recent history of heroin use (N=39)	Males: N=32 Age (years): M=45 (range: 22 to 58) Type of naloxone administered at last witnessed OD: IN (n=31), IM	• Several participants reported struggling to assemble their IN naloxone kit. • Most followed what they had been told in the training about giving half a dose of IN naloxone in each nostril and then waiting before re-dosing. • If the first dose did not revive the victim,

Author (Year), Country	Study Design	Population	Sample Characteristics	Findings Regarding IN Naloxone
			(n=5), none (n=3)	participants usually said that they had administered a second dose. However, there was considerable variability in the length of time participants left between doses (0 to 15 minutes). • Even when participants remembered that they had been told to wait between doses, they often gave the second dose immediately because the victim did not regain consciousness instantly and that worried them. Sometimes, a second or third dose was given ('to be on the safe side') even though the victim had already regained consciousness. • Occasionally, participants rationalized that the victim needed two doses of IN naloxone because they had used a large quantity of drugs, and a few stated that if the victim became angry because they went into withdrawal, that would 'just be too bad'.
Ray (2015), USA[46]	Survey administered following IN naloxone training	Police officers (N=117)	Number of years served as an officer: M=17.26 (SD=9.09) Present at the scene of opioid overdose in the past year (93.2%), past month (49.6%), or sometime within the past three months 46.2%	Following the IN naloxone training: • All of the respondents indicated that the IN naloxone training was not difficult. • 89.7% reported that it would not be difficult to use IN naloxone at the scene of an overdose. • 94% felt that it would not be difficult to train civilians to use IN naloxone. • 82.9% felt that it was important that other officers be trained to use IN naloxone.
Schartel (2018),	Survey administered	First-year student pharmacists (N=59)	NR	Following the IN and IM naloxone training: • 96.6% were confident in their ability to

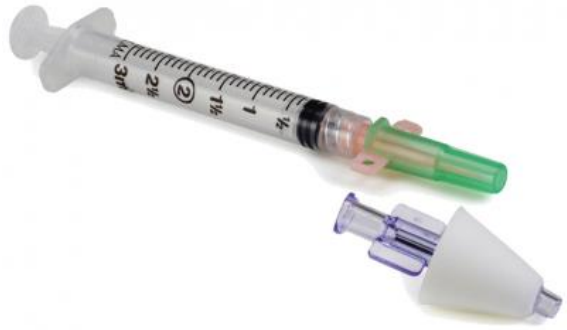
Author (Year), Country	Study Design	Population	Sample Characteristics	Findings Regarding IN Naloxone
USA[47]	following IN naloxone training			administer IN naloxone, compared to 93.2% being confident in administering IM naloxone. • 93.2% were confident in their ability to counsel patients regarding the use of IN naloxone, compared to 88.1% being confident in administering IM naloxone.

Abbreviations: GP: general practitioner; IM: intramuscular; IN: intranasal; M: mean; N: number; NR: not reported; OD: overdose; RCT: randomized controlled trial; USA: United States of America

7.3.2 Narrative Synthesis of Qualitative Data

One qualitative research study (Neale et al., 2019) was included in the review.[40] It was published in 2019 and was conducted in the United States as part of a larger randomized controlled trial (RCT) that examined overdose education and naloxone distribution. Participants were offered a choice between IM naloxone (1 mL naloxone vial + syringe [3 cc/mL, 22G]) and IN naloxone (multi-step atomized nasal spray: 2mg/2 mL Luer-Jet™ Luer-Lock needleless naloxone syringe plus mucosal atomizer device [MAD-300]). It should be noted that the IN naloxone kit examined in this study was a multi-step atomizer spray which may not be reflective of the devices currently available on the Canadian market (e.g., NARCAN® single-step spray). A photo of a multi-step atomized nasal spray similar to the one used in the study is provided in Figure 122. Interviews were conducted with 39 participants with a recent history of heroin use (32 men and 7 women; mean age of 45 years) who had been present at an overdose within the past two months. Naloxone was reported to be administered to relatives, partners, friends, acquaintances, and strangers. Thirty-six of the participants administered naloxone using either the IN (n=31) or the IM (n=5) formulation.[40]

Figure 12. Multi-step Atomized Nasal Spray



Source: Emergency Medical Products[48]

The two aspects of IN naloxone administration noted by Neale et al. were kit assembly and ability to follow administration instructions.[40] Notably, assembly of the IN kit was reported to be a struggle by several participants. With respect to administration, it was reported that participants who used IN naloxone generally followed administration instructions that they had received during training (i.e., to administer half of the dose of the naloxone in each nostril and to wait before re-dosing); most administered a second dose if the first dose did not revive the overdose

victim.[40] However, the length of time between each dose was reported to range from 0 to 15 minutes (recommended time for the multi-step atomizer device was not reported in the study). It was reported that some participants administered the second dose right away if they observed that the first dose did not instantly revive the overdose victim despite remembering being told to wait between doses. It was also reported that some participants administered second or third doses despite the overdose victim having regained consciousness, "to be on the safe side." As one participant noted: *"She was breathing, but it was very, very labored, so that's why I administered the second one [dose]. Because she didn't come out of it with the first one."* Lastly, it was reported that some participants who administered the second dose felt that it was needed due to the large quantity of drugs consumed by the overdose victim; some stated that if the overdose victim became angry as a result of going into withdrawal from the naloxone, that would "just be too bad."[40]

7.3.3 Narrative Synthesis of Survey/Quantitative Data

Three studies were identified that reported survey or quantitative data related to patient perspectives on IN naloxone.[42-44] Across the two studies that compared IN naloxone to other formulations (e.g., injectable), IN naloxone was reported to be the preferred method of administration.[42,43] IN naloxone was deemed to be preferential over other routes of administration for reasons including: ease of administration, reduced blood-borne viruses risk, eliminating the need to carry needles/syringes, painlessness, vein preservation, and less alarming public use.[43] In a study that examined patients' perceptions of IN naloxone specifically, it was reported that patients generally knew what it was used for (65%), but did not know how long it lasts (79%) or where to access it (67%).[44] Across these patients, it was reported that almost all (99%) would be willing to be more open with a provider that distributes IN naloxone; and 58% felt that having IN naloxone may change their behaviours regarding opioid use.[44]

Five studies reported survey or quantitative data related to provider perspectives on IN naloxone.[41,44-47] Across these studies, three examined provider perspectives towards IN naloxone more generally.[41,44,45] Compared to other naloxone delivery routes, IN naloxone was reported to be the preferred method of administration by GPs.[41] In another study examining its use in advanced paramedic trainees, IN naloxone was reported to be easy and safe to administer, more so than IV

naloxone.[45] Lastly, in a study that focused on perspectives of various providers (e.g., physicians, physicians' assistants), almost half felt that availability of IN naloxone kits compared to no naloxone would decrease the likelihood of a future overdose event occurring and would decrease riskier use patterns.[44] However, only 24% of the providers reported completing an IN naloxone-training course, and only 20% felt they knew where to refer patients for IN naloxone kits.[44] Although 96% accurately stated IN naloxone's purpose to treat overdose from any type of opiate or opioid, only 41% were able to correctly identify the duration of action of IN naloxone to be up to 60 minutes.[44]

Two of the studies focused on provider perspectives following an IN naloxone training course.[46,47] In a study of police officers, it was reported that IN naloxone training was not difficult (100%), that it is important that other officers be trained to use IN naloxone (82.9%), that it would not be difficult to use IN naloxone at the scene of an overdose (89.7%), and that it would not be difficult to train civilians to use IN naloxone (94%).[46] In a study of first-year pharmacists, following IN and IM naloxone training, most were confident in their ability to administer IN naloxone (96.6% compared to 93.2% for IM naloxone), and most were confident in their ability to counsel patients regarding the use of IN naloxone (93.2% compared to 88.1% for IM naloxone).[47]

7.4 Conclusions

The systematic review of patient and care provider perspectives on naloxone administration found that IN emerged as the preferential route of administration across both the patient and provider studies that examined it in comparison to other delivery routes. Reasons for this preference provided by patients included ease of administration, reduced blood-borne viruses risk, eliminating the need to carry needles/syringes, painlessness, vein preservation, and less alarming public use.[43]

Eight studies were included in the systematic review of patient and provider perspectives. The qualitative study (Neale et al. 2019) examined perspectives on IN and IM naloxone across participants who had recently been present at an opioid overdose.[40] Most participants were reported to follow IN naloxone administration instructions they had received during training, but

some reported struggling to assemble their IN naloxone kit. It should be noted that the IN naloxone kit examined in the Neale et al., 2019 study was a multi-step atomizer spray which may not be reflective of the devices currently available on the Canadian market (e.g., NARCAN® single-step spray). Reasons for deviating from administration instructions included worry over the overdose victim not regaining consciousness immediately, needing to confirm that the naloxone was effective ("to be on the safe side"), and large quantity of drugs consumed by the overdose victim. Across the survey/quantitative data studies, three reported on patient perspectives and five reported on provider perspectives on IN naloxone. Across the studies examining IN naloxone training for providers, IN naloxone was reported to be easy to use by almost all participants.

Overall, the systematic review of patient and care provider perspectives on IN naloxone administration suggests that IN naloxone appears to be the preferred route of administration for both patients and providers. As a result, IN naloxone appears to be appropriate for dissemination for public and provider use. However, given the scarcity of the qualitative literature, further research on patient and care provider perspectives in this area is warranted.

8 Cost-Effectiveness Analysis Comparing Intranasal and Intramuscular Naloxone

Summary

- This analysis compares costs and reversal outcomes between IN and IM routes of naloxone for suspected opioid overdoses when administered by bystanders and first responders.
- The base case analysis examined the short-term costs and outcomes from naloxone administration as an incremental cost effectiveness ratio (ICER) with cost per reversal as the outcome. IN had higher cost and equivalent or lower effectiveness than IM naloxone, and was therefore dominated (ICER: -$807.66/reversal; 95% CI: -$983.80 to -$683.42).
- The cost-effectiveness of IN compared to IM naloxone is sensitive to bystander and first responder willingness to administer.
- The lifetime time horizon scenario analysis found that IN naloxone is equivalent to IM naloxone. For both routes of administration, mean costs and QALYs were within the 2% margin of error introduced through probabilistic analysis.

8.1 Purpose

To estimate the cost-effectiveness of intranasal (IN) versus intramuscular (IM) community-based naloxone for the treatment of opioid overdoses by public bystanders and first-responders in Alberta from the perspective of the provincial publicly funded health care system. An Excel file entitled “Naloxone CEA.xlsm” accompanies this analysis and allows the user to adjust model inputs as required and data becomes available (Figure 13). The base case analysis and all scenarios are adjustable through inputs on the “Cover” sheet and the “Inputs” sheet. For the purpose of this analysis, the term ‘first responders’ refers to fire fighters and law enforcement officers that are trained to administer naloxone in their professional capacity but are not health professionals (i.e. dual-trained firefighter-paramedics).

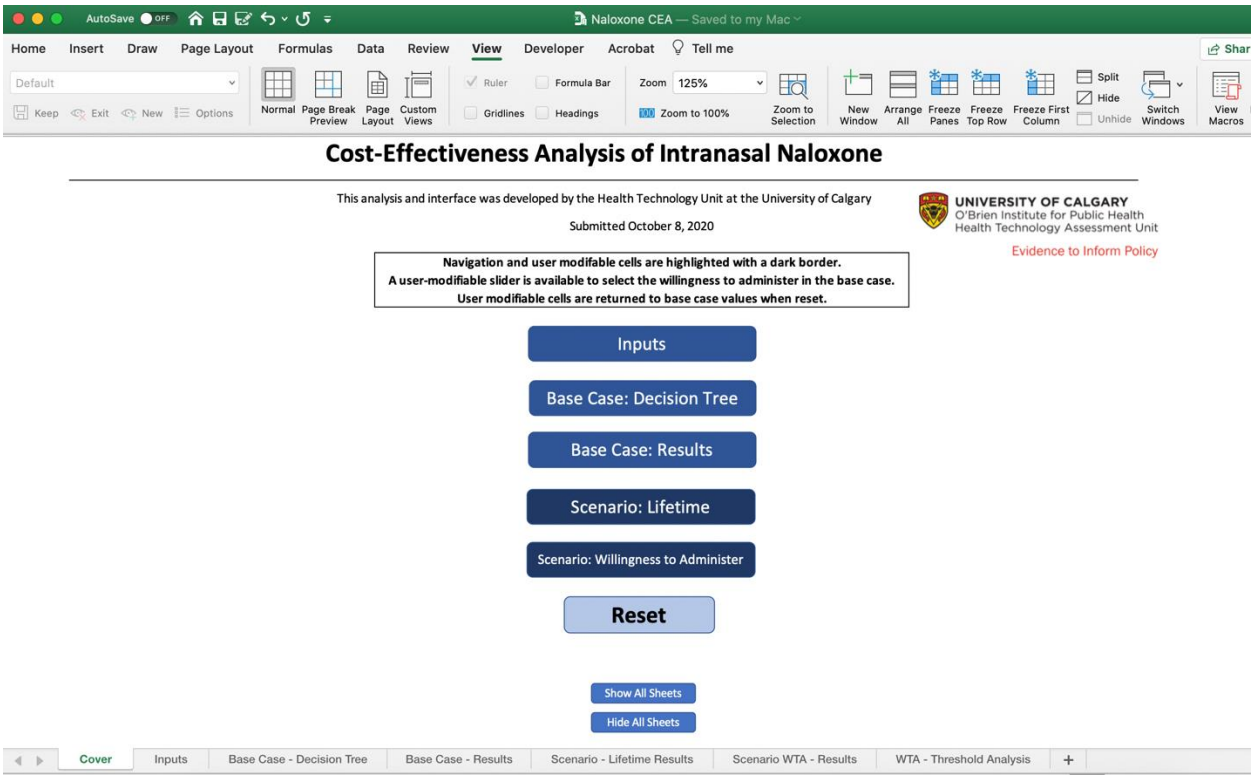


Figure 13. “Naloxone CEA.xlsm" Screenshot

8.2 Methods

8.2.1 Model Overview

In the base case analysis, a decision tree model is used. The target population is people who have overdosed on an opioid and a bystander or first responder with a naloxone kit is present. This analysis considers IN and IM administration routes, both of which are available and used for the treatment and reversal of opioid overdoses in Alberta.

The provincial community-based naloxone (CBN) program was implemented in December 2015 with IM naloxone dispensed publicly allowing public access to kits and training at registered sites, including community pharmacies, harm reduction agencies, and Indigenous organizations.[49] IM naloxone is now dispensed publicly at 2,093 registered sites in Alberta.[50] A February 2017 Ministerial Order gave non-regulated first responders, including police officers and fire fighters, the ability to administer IM naloxone following training.[51] Through the Alberta Health Services Medical First Response (MFR) program, registered agencies receive IM injection kits at no cost to the agency, whereas IN kits may be purchased by the agency and then

reimbursed following administration.[52] Police services are reimbursed for the purchase of IN naloxone kits up to the cost of an IM kit.[53] As IM naloxone is the funded route of CBN and provided to MFR agencies and police services, it is used as a reference case.

8.2.2 Base Case

The base case examines cost per reversal using a decision tree with IN and IM naloxone administration route treatment arms (Figure 14). The change in estimated costs between IN and IM administration routes is divided by the difference in the probability of overdose reversal to calculate the cost per reversal as an incremental cost-effectiveness ratio (ICER):

$$\text{Incremental Cost per Reversal} = \frac{(\text{Cost IN} - \text{Cost IM})}{(\text{Reversal Probability IN} - \text{Reversal Probability IM})}$$

In the base case a time horizon of one hour was considered. A discount rate for costs was not applied, following the Canadian Agency for Drugs and Technologies in Health guidelines.[54]

Probabilistic sensitivity analyses (PSAs) were performed to examine parameter uncertainty, deterministic estimates are also selectable. To capture parameter uncertainty, outcome parameters including probability of reversal and probability of supplemental naloxone required, were assigned distributions. Costs were not assigned distributions as no data on cost distributions were obtained, estimated values are user-modifiable. IM naloxone reversal probabilities and supplemental naloxone required are non-negative in this analysis and range from zero to one, therefore a beta distribution was assigned to these parameters. To allow for variance in IN naloxone outcomes, risk ratios from the meta-analysis were assigned lognormal distributions. Model convergence, defined as less than a 2% deviation in mean costs and outcomes between model runs, was realized with 1000 successive Monte Carlo simulations. The ICER 95% confidence intervals were calculated using the Fieller method in STATA 16.[55] A cost-effectiveness planes with 95% confidence ellipses were generated with R Statistical Software.[56]

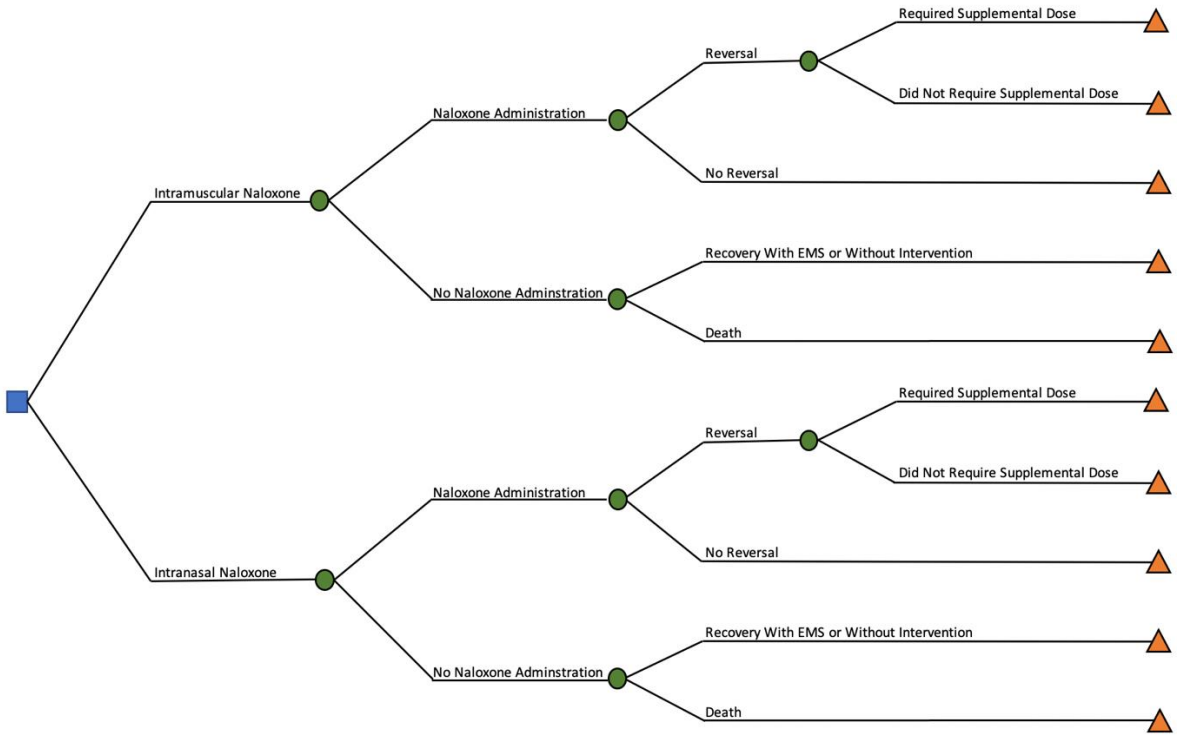


Figure 14. Decision Tree Model Diagram

8.2.3 Model Inputs

Meta-analyses of probability of reversal and requirement of supplemental naloxone from the clinical effectiveness systematic review was used to inform model inputs (

Table 8). This analysis uses evidence from the meta-analysis performed in the clinical effectiveness systematic review, randomized controlled data, and Alberta-specific costs for model inputs. Kerr et al. (2009)[57] was the only study to consider IM vs IN; other studies in meta-analysis included intravenous administration of naloxone, which is not a method of administration likely to be used by first responders without medical training. From these results, a risk ratio of 0.93 (95% CI: 0.78; 1.11) was calculated and used in the model to allow for parameter uncertainty.

Table 8. Model Inputs for the Base Case Analysis

Parameter	Value	Standard Error	Distribution	Source
Reversal				
IM Probability of Reversal	0.775	0.04	Beta	RCT[57]
Risk Ratio: IN vs. IM	0.93	0.09*	Log-Normal	RCT[57]
Supplemental Naloxone Required				
IM Probability	0.083	0.017	Beta	Meta-analysis (Section 6)
Risk Ratio: IN vs. IM	2.59	0.24*	Log-Normal	Meta-analysis (Section 6)
Mortality				
Probability without naloxone administration	0.111	0.02	Beta	Meta-analysis[58]
Willingness to Administer Naloxone				
Probability	0.884	0.11	Beta	Lagu (2006)[53]

*SE[ln(RR)]; RCT = randomized controlled trial

The probability that naloxone was administered was included in model and captures the willingness of bystanders and non-EMS first responders to administer naloxone. In the base case analysis, it is assumed that there is no difference in the willingness-to-administer naloxone between routes. There are no Alberta or Canada-specific estimates for the willingness of bystanders or first responders to administer naloxone to a person experiencing a suspected opioid overdose. It is assumed that there is variability in the willingness-to-administer naloxone geographically, by drug user status, and by those who selected to obtain a kit.[59,60] Lagu et al. (2006)[59] surveyed 329 people using drugs and found that 88.4% would be willing to administer naloxone to an overdosed colleague and is applied to both IN and IM administration routes in the model.

In overdoses that were reversed with naloxone administration it was found in meta-analysis that it was over two times more likely that a supplemental dose would be required in persons administered IN naloxone. The risk ratio of requiring supplemental naloxone was 2.59 (95% CI: 1.63; 4.12), suggesting that IM administration requires less frequent supplemental doses. Studies did not standardize the number, route, or dose of supplemental naloxone administered. Studies inconsistently identified if supplemental doses were administered when no reversal occurred. Therefore, it was assumed if no reversal occurred following an initial dose, supplemental naloxone was administered. Community-based naloxone kits are supplied with three 0.4 mg IM naloxone doses while IN naloxone kits are commonly supplied with two 4 mg nasal atomizers.[53] Community-based naloxone kits recommend repeating IM injections until help arrives.[61] It was assumed that if person required a supplemental dose they received the remaining naloxone available in the kits available in Alberta; two supplemental doses for IM and one for IN. The model assumes that when supplemental doses of naloxone are required for reversal, and where there is no reversal, that all doses in a kit are administered.

The "no naloxone administration" branches include recovery or death terminal nodes. Evidence of mortality in bystander-witnessed opioid overdoses is from Giglio et al. (2015)[58] where a meta-analysis was performed on a total sample of 66 overdoses and found a mortality rate of 0.111 when naloxone was not administered. This input is aligned other studies that applied mortality rates of approximately 10% for overdoses without naloxone administration.[62,63]

Costs are considered from the perspective of Alberta Health, the public health care payer. The costs of community-based naloxone kits are variable based on quantity ordered and negotiations with suppliers. The costs are summarized in Table 9. A single dose of IN naloxone ranges between $42 and $63.70 and a kit contains two doses. A three-dose IM naloxone kit costs between $32 and $36.[18] As these costs are dependent on quantity ordered and negotiated with suppliers, the cost input is user modifiable. The base case assumes the lowest price available for both IN and IM administration routes. This analysis assumes the full-price of naloxone kits are the responsibility of the public health care payer. To explore wastage, supplemental doses of naloxone are used to estimate the doses required per patient. For patients that experience a reversal with supplemental doses or do not experience successful reversal, it was assumed that

the entire kit would be used. For patients that do not receive naloxone, there was no use of naloxone. In the accompanying model, the cost input can be modified by the user to be shown as a cost per kit, in place of a cost per dose to inform on wastage associated with the practice of replacing kits instead of doses following use.

Table 9. Costs of Intramuscular and Intranasal Naloxone

Administration Route	Doses per Kit	Cost per Kit	Distribution	Source
Intramuscular	3	$32.00 to $36.00	Fixed	Alberta Health
Intranasal	2	$84.00 to $127.40	Fixed	Alberta Health

8.2.4 Scenario Analyses

8.2.4.1 Willingness to Administer

There is no evidence to inform differences in willingness of first responders to administer naloxone based on route and weak evidence to inform the willingness of bystanders or first responders to administer naloxone to a suspected opioid overdose.[59,86] Thus, a scenario analysis was performed that examined a threshold of willingness to administer IM naloxone to a person with a suspected opioid overdose compared to IN naloxone to a suspected overdose patient.

8.2.4.2 Lifetime Time Horizon

To extend the decision tree to the lifetime time horizon and examine quality adjusted life year outcomes, Markov models were linked to each of the terminal nodes of the decision tree. This model extension draws upon on the work of Cipriano et al.[62] Standard half cycle correction was applied, which assumes that transitions happen at the midpoint of each model cycle.[64] Discount rate of 1.5% was applied to costs and QALYs, which is congruent with Canadian Agency for Drugs and Technologies in Health economic evaluation guidelines.[65] Perspective is the same as that taken for the decision tree.

Similar to Cipriano et al. (2018),[62] it was assumed that 100% of individuals would have a substance use disorder. Health states were: substance use disorder without treatment, substance use disorder with treatment, and death (Figure 15). Twenty-three percent of individuals would

receive treatment for their substance use disorder, and the remainder would not.[66] From the substance use disorder health states, the only possible transition was to the death state.

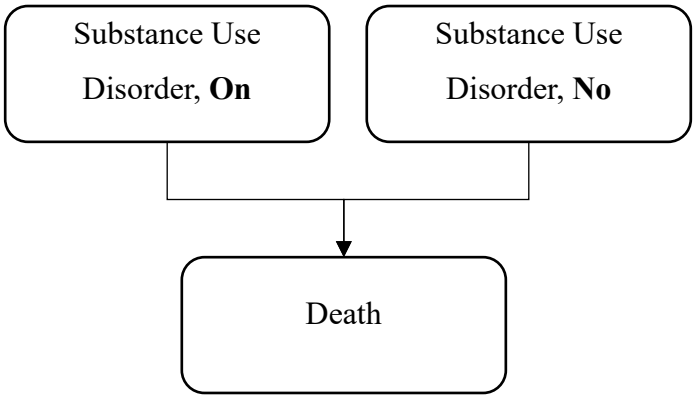


Figure 15. Markov Model Structure for Lifetime Time Horizon, Appended to Each Terminal Node of Decision Tree

Following overdose in the decision tree, the probability of having Emergency Medical Services (EMS) called was 0.56.[67] This value reflects the probability that EMS was called following use of a take home naloxone kit in British Columbia[67] – no such estimate was available for Alberta. When EMS was called, patients were assumed to be taken to the Emergency Department (ED), with 45% of patients being discharged directly from the ED.[68] If no reversal occurred in the decision tree, it was assumed that EMS was called and the patient was admitted to hospital. If the patient was not discharged from the ED, it was assumed that the patient was admitted to hospital.

The patient considered in the model was assumed to be 38 years old, which reflects the average age of Albertans in 2019.[69] Transition to the death state for all patients reflects age-specific mortality in Alberta as of 2018,[70] with additional assumptions based on initial opioid overdose and subsequent health states. For patients that did not experience successful opioid effect reversal in the decision tree following naloxone administration, mortality on the first day was elevated by 11.9%.[71] Rando et al. (2015)[71] reports mortality for 7 out of 59 (11.9%) patients that were not lost to follow-up following police administration of naloxone. For patients that did not have naloxone administration, mortality on the first day was elevated by 11.1%.[72] Giglio et al.

(2015)[72] reports mortality in 3 out of 27 patients that had a witnessed opioid overdose where naloxone was not administered. For the remainder of the first year following overdose, mortality for all patients was elevated by 9.9%.[73] Relative risk of mortality for patients with substance use disorder without treatment was 14.68, which was multiplied by age-specific mortality during each cycle.[74] Compared to those without treatment, relative risk of mortality for patients with substance use disorder on treatment was 0.42.[75]

During each cycle, utility associated with health states was based on estimates of age-specific utility in Alberta, generated with the 2013-14 Canadian Community Health Survey.[76] Compared to age-specific norms in Alberta, the multiplier of 0.8 was applied to utility in those with substance use disorder.[77] The multiplier of 1.07 was applied to the utility of those with substance use disorder for treatment.[77]

Costs over the lifetime time horizon start immediately after the decision tree. The cost of having EMS called was $964.56.[78] If EMS was called, it was assumed that the patient was transported to the ED, incurring costs of physician assessment and hospital costs. Patients that were admitted to hospital incurred additional costs: physician admission costs, case-mix grouper costs for the admission, and daily physician consultation costs. Like Cipriano et al. (2018),[62] the Comprehensive Ambulatory Classification System (CACS) cost for "Addiction/Substance Abuse"[79] and the Case Mix Grouper (CMG) plus Cost for "Poisoning/Toxic Effect of Drug"[80] was used; both with 2018 costs inflated to 2020 CAD, which was the most recent costs available in Alberta. The same combinations of physician billing codes were assumed for hospitalizations as Cipriano et al. (2018).[62] After the initial hospitalization, if it occurred, patients experience annual age-specific health care costs in Alberta, with multiplicative effects for substance use disorder on treatment, and substance use disorder without treatment. Costs of EMS care, ED department costs, inpatient services hospital costs, ED cost for MD services, and length of stay were assumed to be correlated. In probabilistic analyses, these costs were represented by a normal distribution with mean of 1 and standard deviation of 0.5. The same approach was used by Cipriano et al. (2018).[62]

Over the lifetime time horizon, age-specific costs for Albertans were used, from the Canadian Institute for Health Information (2019).[81] A multiplier for substance use disorder of 2.32 was applied, which was estimated with mean costs of opioid using Medicaid patients, relative to abstaining Medicaid patients.[82] For those patients on treatment for substance use disorder, a cost reduction of 29% was applied, relative to patients not on treatment for substance use disorder.[83]

All additional model inputs required for the lifetime time horizon are detailed in

Table 10. In probabilistic analysis, lognormal distributions were used to represent relative risk variables, which assumes that relative risk is normally distributed on the logarithmic scale.[84] All other variables were represented with normal distributions, which may be considered for representation of any variable due to the central limit theorem.[85]

Table 10. Additional Model Inputs for Lifetime Time Horizon

	Model Input	Mean (SD)	Probabilistic Distribution	Source
Connecting decision tree to Markov Model	Starting age	38 (NA)	Fixed	Government of Alberta[69]
	Probability EMS is called	0.56 (0.01)	Normal	Karamouzian et al. (2019)[67]
	Probability of discharge from ED	0.45 (<0.01)	Normal	Yokell et al. (2014)[68]
Mortality	Age-specific mortality	Age-dependent	Fixed	Statistics Canada[70]
	Mortality on day 1 for patients that do not experience initial opioid reversal	0.12 (0.04)	Normal	Rando et al.(2015)[71]
	Mortality on day 1 for patients that do not have naloxone administered	0.11 (0.06)	Normal	Giglio et al. (2015)[72]
	Elevated mortality risk over remainder of first year, all patients	0.10 (<0.01)	Normal	Weiner et al. (2017)[73]
	Relative risk of mortality, substance use disorder	14.68 (0.06)*	Lognormal	Mathers et al. (2013)[74]
	Relative risk of	0.42 (0.15)*	Lognormal	Degenhardt et al.

	mortality, substance use disorder on treatment			(2010)[75]
Utility	Age-specific utility	Age-dependent	Normal	Guertin et al. (2018)[76]
	Utility multiplier for substance use disorder	0.8 (0.05)*	Lognormal	Coffin & Sullivan (2013)[77]
	Utility multiplier for substance use disorder on treatment	1.07 (0.03)*	Lognormal	Coffin & Sullivan (2013)[77]
Costs	Cost of EMS call	$964.56	Normally distributed, correlated with other healthcare costs	Alberta Health Services (2019)[78]
	ED Cost	$504.76		CACS Code E701 - Addiction/Substance Abuse[79]
	ED cost for MD services	$99.19		Government of Alberta - Code 03.04F[69]
	Inpatient hospital costs	$9,889.63		CMG+ Poisoning/Toxic Effect of Drug[80]
	Length of Stay	3.76		CMG+ Poisoning/Toxic Effect of Drug[80]
	If admitted, inpatient MD cost for admission assessment (assumed Internal Medicine specialty)	$198.70 (NA)	Fixed	Government of Alberta - Code 03.04C[69]
	Inpatient MD cost for consultation (Internal Medicine specialty)	$198.70 (NA)	Fixed	Government of Alberta - Code 03.08A[69]
	Inpatient MD bill per day for repeat consultations, applied on all days other than day of admission (Internal Medicine specialty)	$154.99 (NA)	Fixed	Government of Alberta - Code 03.07B[69]
	Age-specific costs of healthcare in Alberta, applied annually	Depends on Age	Fixed – no estimate of variability available	Canadian Institute for Health Information[81]
	Cost-multiplier for substance use	2.32 (NA)	Fixed – no estimate of	White et al. (2011)[82]

	disorder, applied to age-specific healthcare costs		variability available	
	Cost reduction for treatment of substance use disorder, relative to substance use disorder	0.29 (<0.01)	Normal	Baser et al. (2011)[83]

*SE[LN(RR)] is the measure of spread

8.3 Results

8.3.1 Validity

This model represents a theoretical treatment pathway and is based on published economic evaluations of naloxone for the treatment of suspected opioid overdoses.[63] To assess internal validity, adjustments were made to model inputs and changes to model outputs in the expected direction and of the expected magnitude were evaluated. All modelling was independently verified by a second health economist. External validity could not be assessed, as there are no comparable models.

8.3.2 Base Case Analysis

The base case examines the hour immediately following a suspected opioid overdose. The estimated probability of reversal was equivalent between treatments and more costly with IN naloxone when compared to IM (

Table 11). Consequently, IN was dominated by IM naloxone when administered by bystanders and first responders for the reversal of an opioid overdose. These differences in cost and effectiveness are clearly depicted in Figure 16. IN economic outcomes are directly above IM in Figure 16, due to increased costs, and the horizontal position (which indicates probability of reversal) is the same for both treatments.

Table 11. Base Case Scenario Analysis Results

Administration Route	**Mean Cost (95% CI)**	**Mean Probability of Reversal (95% CI)**	**ICER (95% CI)**
Intranasal	$53.06 ($39.30 to $66.82)	0.637 (0.445 to 0.828)	
Intramuscular	$14.92 ($11.07 to $18.78)	0.684 (0.503 to 0.864)	**DOMINANT -$807.66/reversal (-$983.80 to -$683.42)**

Note. The negative ICER indicates that IN is more expensive and less effective than IM.

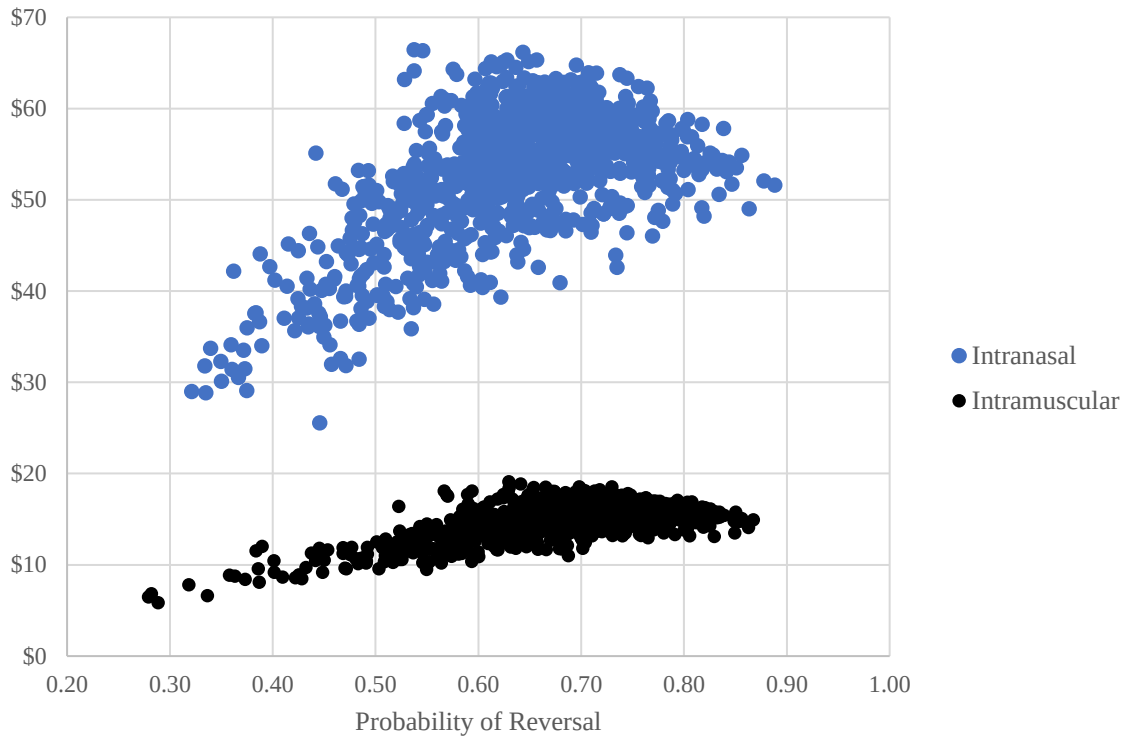


Figure 16. Estimated Costs and Probability of Reversal with IN and IM Naloxone

The cost-effectiveness plane is shown in Figure 177 with a 95% confidence ellipse. Simulation results are concentrated in the top left quadrant where there are higher costs and lower likelihood of reversal for IN compared to IM. Cost per reversal thresholds of $1000, $400, and $100 per reversal are shown for reference.

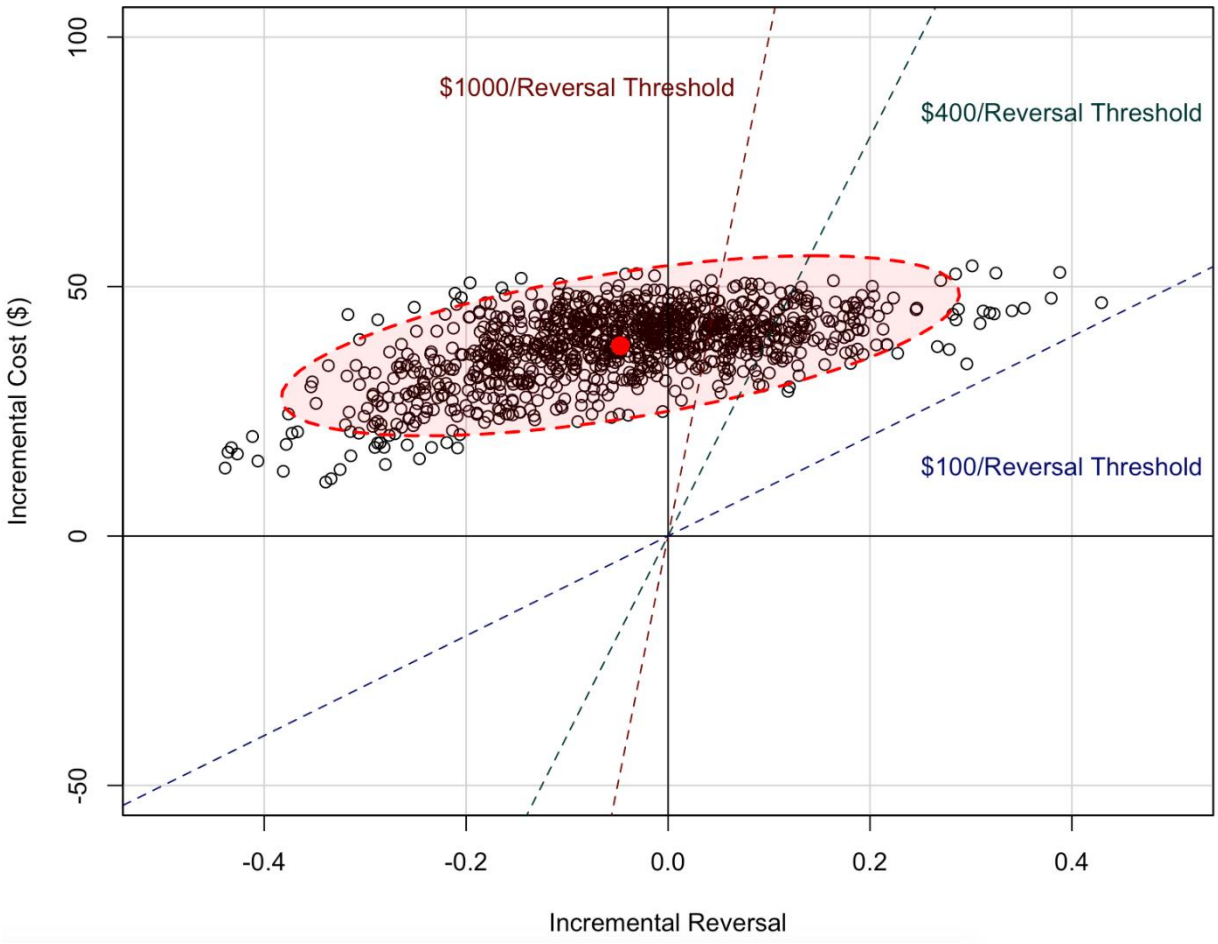


Figure 17. Cost-effectiveness Plane of IN Compared to IM Naloxone Administration Routes with 95% Confidence Ellipse

8.3.3 Scenario Analyses

8.3.3.1 Willingness to Administer

When there is 88% willingness to administer both IN and IM naloxone, the ICER is estimated as -$827.18 per reversal for IN when compared to IM; IN naloxone is less effective than the IM route, with IN remaining the more costly option.

The threshold analysis examines the effect that a decrease in the willingness to administer IM naloxone has on the incremental cost per reversal while IN remains constant at 0.88 (with bystanders and first responders 88% willing to administer IN naloxone). It is observed that the estimated incremental cost per reversal becomes positive when the difference in the willingness

to administer naloxone is greater or equal to 0.06 between IN and IM, with an ICER of $94,498.55 per reversal for IN compared to IM at 0.06.

The results of this scenario analysis suggest that the incremental cost per reversal is dependent upon the willingness of the bystander to administer naloxone. With a difference of willingness to administer naloxone between 0 and 0.06, IN is dominated by IM naloxone. Above the threshold value of 0.06 for the difference in willingness to administer naloxone, IN is more expensive and more effective than IM, as shown in Figure 188.

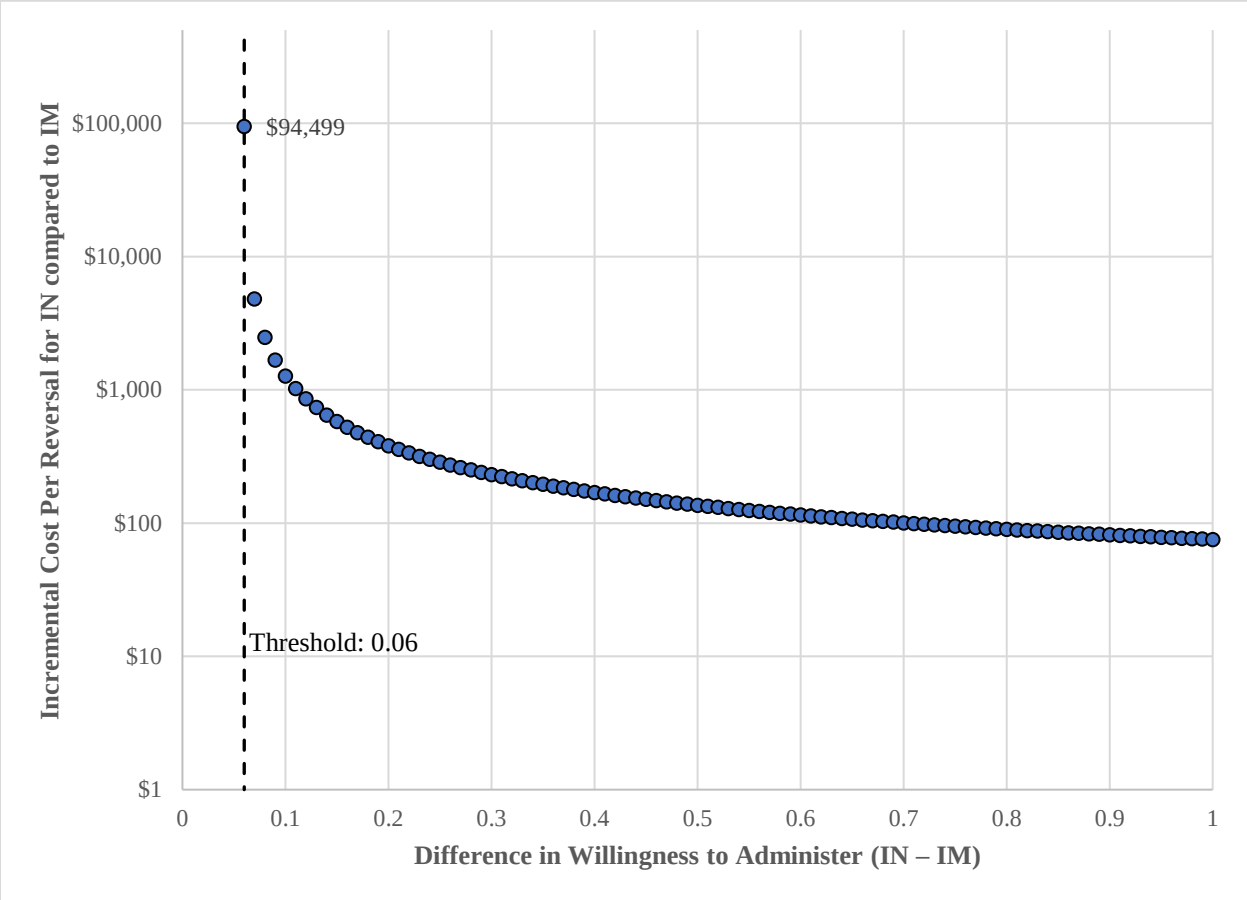


Figure 18. Cost-effectiveness Threshold Analysis of IN versus IM Naloxone as a Function of Difference in Willingness to Administer

This scenario analysis found that small differences in willingness to pay have large impacts on the incremental cost per reversal. For example, in the scenario where bystanders are willing to

administer IM naloxone in 58% of overdoses compared to 88% with IN, it is found that for IN naloxone to have a positive ICER, the cost threshold per reversal is estimated to be $231.58.

8.3.3.2 Lifetime Time Horizon

Over the lifetime time horizon, IM is estimated to result in the same QALYs the same cost as IN (Table 12 and Figure 19). Confidence intervals overlap almost completely, suggesting there is no significant difference in outcomes between administration methods over the lifetime time horizon. In probabilistic analysis with distributions fit to each model parameter, model convergence is used to assess whether sufficient Monte Carlo simulations have been conducted. In this analysis, convergence was defined as less than 2% variation in mean model outcomes following successive simulations – and was achieved at 1,000 simulations. For each treatment, mean cost and QALYs are within 2% of each other. This means that model outcomes overlap so completely that they should be considered indistinguishable from each other. In the cost-effectiveness plane in Figure 20, this result is visually demonstrated.

Table 12. Lifetime Time Horizon Results

Administration Route	**Mean Cost (95% CI)**	**Mean QALYs (95% CI)**	**ICER (95% CI)**
Intranasal	$126,238 ($125,676 to $126,801)	9.701 (9.661 to 9.741)	–
Intramuscular	$126,483 ($125,938 to $127,029)	9.769 (9.728 to 9.809)	**Equivalent**

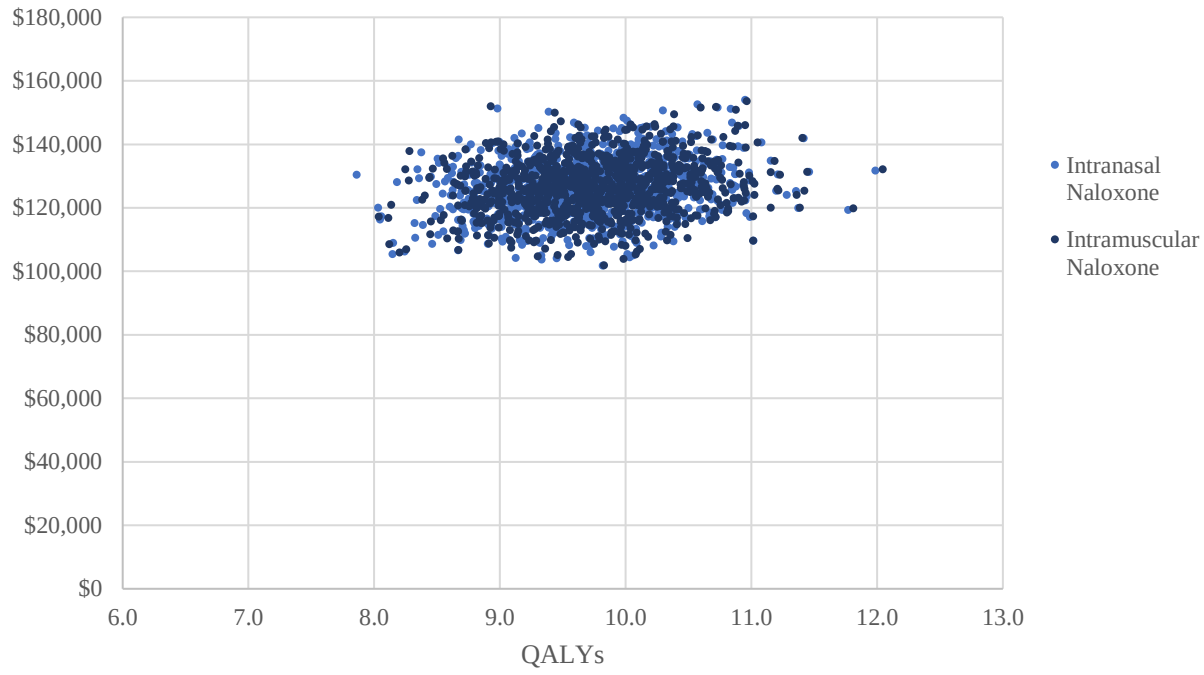


Figure 19. Outcomes of Probabilistic Sensitivity Analysis over the Lifetime Time Horizon

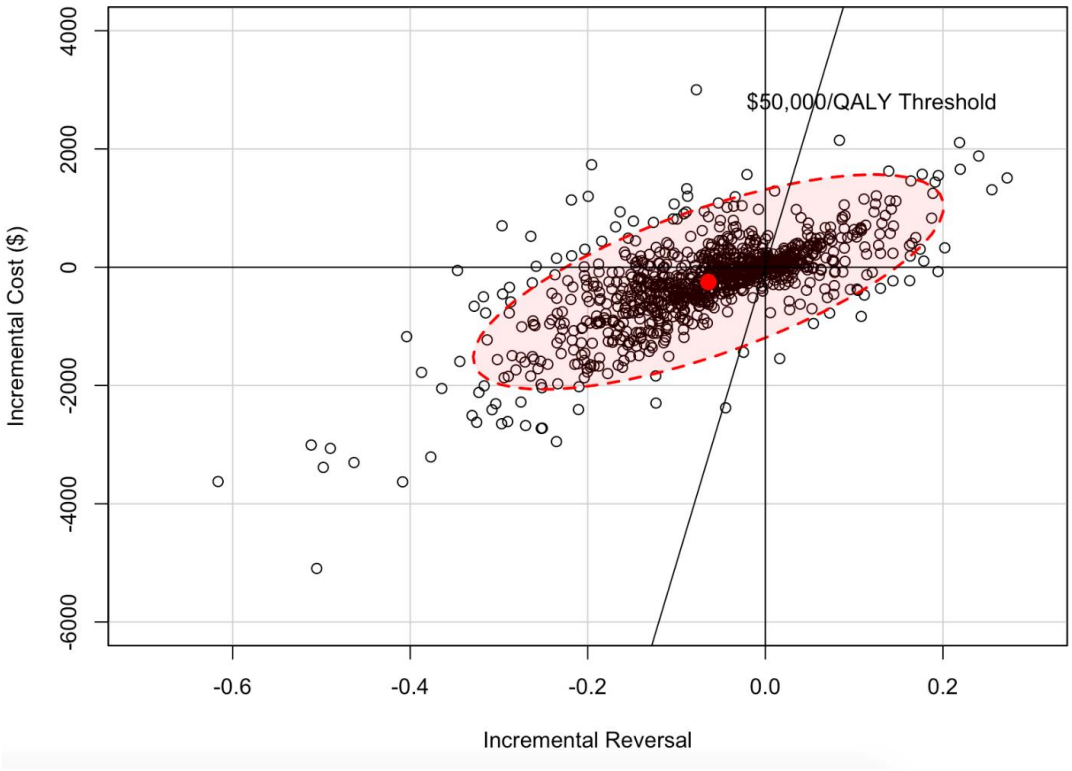


Figure 20. Cost-effectiveness Plane of IN Compared to IM Naloxone Administration Routes with 95% Confidence Ellipse

8.4 Conclusions

In the base case analysis, IN is dominated by IM naloxone. IN costs more than IM, (IN: $53.06 (95% CI: 39.30 to 66.82) versus IM: $14.92 (95% CI: 11.07 to 18.78)) with equivalent effectiveness (IN probability of reversal: 0.64 (95% IC: 0.45 to 0.83) versus IM probability of reversal: 0.68 (95% CI: 0.50 to 0.86)). In scenario analysis it was found that the model is highly sensitive to the willingness to administer naloxone, which is assumed to be equivalent between routes of administration. If the willingness of bystanders and first responders to administer differs by route of administration, IN naloxone may become more expensive and more effective than IM naloxone. And over the lifetime time horizon, differences in cost and QALY outcomes between treatments are equivalent.

While the estimate of willingness to administer is useful to our analysis it should be used cautiously as it does not reflect the increased availability of naloxone for high rates of opioid overdoses experienced recently. Should local estimates of willingness of administration be obtained, the user is encouraged to add them into the model. Data on the willingness of bystanders and first responders in Alberta to administer naloxone, compared by route of administration, would improve the robustness of this model.

This model also included a limited exploration of costs of wastage. It was assumed that supplemental dose(s) of naloxone in randomized controlled trials was equivalent to the use of the entire naloxone kit in this model. Unfortunately, poor reporting of naloxone use in randomized controlled trial inhibits accurate estimate of doses used. The pricing approach of IM, which is per kit, compared to the pricing of IN as per dose also affects the way wastage impacts the cost-effectiveness of each approach. If replacement of naloxone was by dose used there may be opportunity to replace only the amount used and not an entire kit, decreasing wastage.

With a large increase in opioid-related deaths over the previous 5 years there have been investments in surveillance in the health care system. Publicly available surveillance reports of opioid-related deaths, acute care usage, and campaigns for CBN distribution and other harm reduction treatments have contributed to improved understanding of the treatment of opioid

overdoses by the public. Despite advancements there remains a lack of data available for first responder administration. The lack of non-medical first responder administrative data creates barriers to understanding the characteristics of naloxone administration and differences between organizations and geographical areas.

Key limitations affecting this model include the lack of data describing current use and resulting efficacy. If available, the current usage statistics by route of naloxone administration could be used a proxy for willingness to administer. In some cases, reporting of naloxone use may be perceived to result in unwanted exposure to police and the justice system, resulting in potential sampling bias in the data. Increased reporting of naloxone would allow comparison of outcomes estimated in this model to the outcomes achieved in the real world. This model also does not consider dose in the comparison of IM and IN administration routes. In the systematic review of clinical efficacy, insufficient information for meta-regression by dose was encountered. However, it is known that bioavailability, and therefore efficacy, may differ by route of administration.[87] The model is reflective of current naloxone doses available in kits and their respective costs for the treatment of opioid overdoses by bystanders and first responders in Alberta.

This model uses Alberta-specific data and the best available evidence to inform on the cost-effectiveness of different routes of naloxone for the treatment of opioid overdoses by bystanders and first responders. The results of the model are found to be sensitive to the willingness of bystanders and first responders to administer naloxone by different routes. IN naloxone administration was found to be associated with a higher cost when compared with IM in the immediate term, and equivalent costs in the long term. The results of this model suggest that IN naloxone offers no improvement in outcomes, at an additional upfront cost, when compared with IM naloxone for the treatment of opioid overdoses when administered by bystanders or first responders.

9 Budget Impact Analysis

Summary

- The objective of this analysis is to develop an interactive budget impact analysis tool that could be adapted to accommodate future data regarding naloxone kit distribution. The accompanying tool is intended to highlight the relationships between variables, and the user is encouraged to interpret the values of results cautiously.
- Budget impact is predicted for three scenarios for naloxone for the treatment of opioid overdoses by bystanders and non-medical first responders: 1) status quo, 2) technology mix of IN and IM naloxone, and 3) extending expiration dates from 2 to 3 years.
- In all scenarios, IN naloxone is associated with higher costs when compared to IM naloxone.
- In all scenarios considered, the estimated budget impact to the province to distribute naloxone kits over 3 years is approximately $19 million. Scenario one demonstrates how costs to the province increase as the number of naloxone kits distributed increases,
- In scenario two, we see that as the proportion of IN kits distributed increases, the total costs for naloxone increases. Although these costs are not borne by Alberta Health, they would be paid for by the organizations that are delivering and using the naloxone.
- In the third scenario, impacts of extending the shelf life of naloxone kits are explored. This is estimated to increase the number of viable naloxone kits in circulation, at reduced cost to the province.

9.1 Purpose

To develop an interactive budget impact analysis tool that could be adapted to accommodate future data regarding naloxone kit distribution. This budget impact analysis considers scenarios for the funding of naloxone for the treatment of opioid overdoses administered by bystanders and non-medical first responders. Comparative costs of IN and IM administration routes to the publicly funded health care payer are predicted.

9.2 Overview

Three implementation scenarios were developed based on current programs and treatment options. Scenarios include: 1) status quo, 2) technology mix of IN and IM naloxone, and 3) extending expiration dates from 2 to 3 years. The user is encouraged to modify the settings in the accompanying spreadsheet for the consideration of specific scenarios and their related budget impacts.

9.3 Methods

This budget impact analysis was performed over a 3-year time horizon. These time horizons correspond with 2020 as year 0 and 2021, 2022, 2023 as subsequent years. Costs are considered from the perspective of Alberta Health. A user-modifiable Excel spreadsheet is included with this report ("Naloxone BIA.xlsm") that allows the scenarios, strategies, and inputs to be customized (Figure 21).

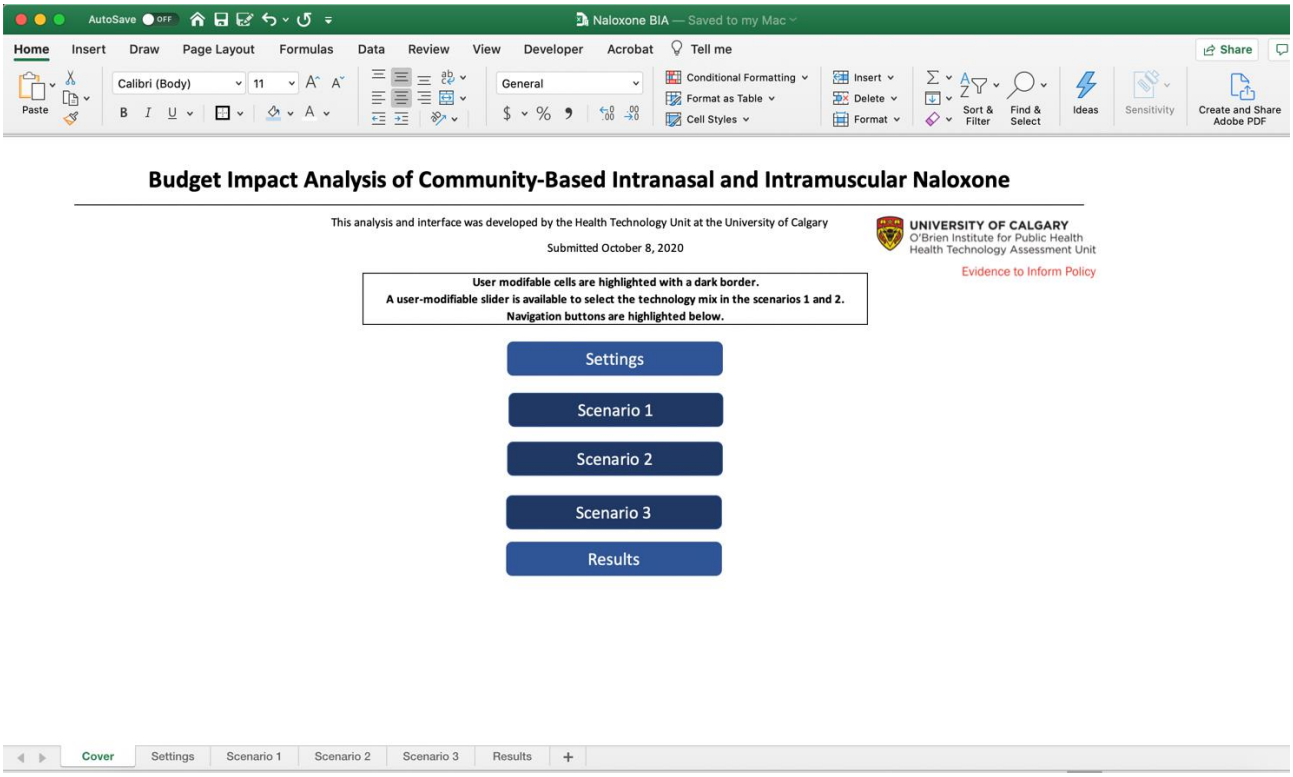


Figure 21. Screenshot of "Naloxone BIA.xlsm"

9.3.1 Eligible Population

To increase access for persons at risk of an opioid overdose, naloxone has been available without a prescription in Alberta since May 2016.[49] Community-based naloxone kits are distributed through AHS Harm Reduction Services from registered sites with no out-of-pocket costs to recipients in Alberta. Community-based IM naloxone kits are dispensed free of charge to individuals and agencies. The Alberta Health Services (AHS) provincial naloxone program

dispensed 271,681 naloxone kits from January 2016 to June 2020, and 18,374 reversals were reported.[50] The annual number of kits dispensed are shown in Table 13.

Table 13. Annual Number of Community-based Naloxone Kits Dispensed

Year	Community-Based Naloxone Kits Dispensed	
2016	9572	
2017	28,165	
2018	84,117	
2019	97,724	
2020*	52,103	
2021	119,454	Projection
2022	127,745	
2023	134,544	
2023	140,309	

*Year to date June 30, 2020

Quarterly reporting from April 1, 2017 to June 30, 2020 of community-based naloxone kits is used to project the number of kits dispensed in Alberta to June 30, 2024 using logarithmic regression with an R^2 of 0.845 (Figure 22). The number of kits dispensed quarterly and the number of overdoses reported varies. Several factors influence the distribution of kits to persons who may witness or experience an opioid overdose. Access to harm reduction services, recipient characteristics, and the characteristics of opiate consumption contribute to the acceptance and distribution of naloxone.[88] Synthetic opioids, including potent fentanyl analogues, may require higher doses of naloxone for reversal.[89] Therefore, predictions of kits distributed and the number of reversals require caution in interpretation.

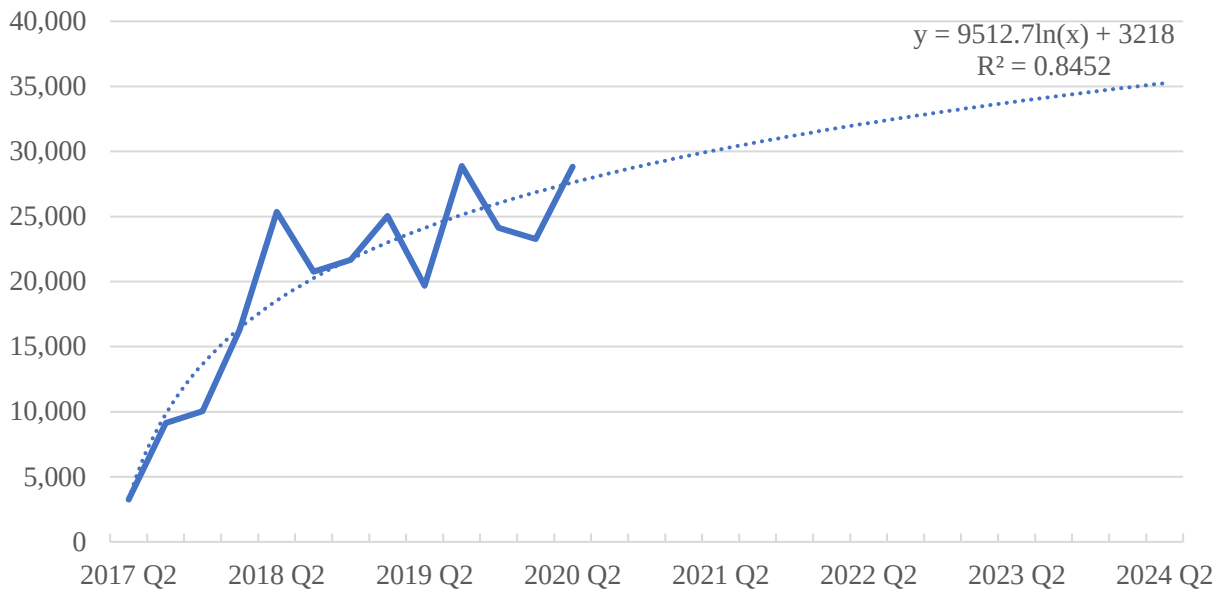


Figure 22. Quarterly Naloxone Kits Dispensed Projected to 2024

First responder agencies may be partially subsidized for IN naloxone from Alberta Health.[90] Police services may purchase the IN naloxone kits at a higher cost than IM naloxone kits and submit for partial reimbursement, up to the cost of the IM naloxone.[6] Fire departments registered with the AHS Medical First Response (MFR) program are eligible for reimbursement of IN naloxone following use.[18,52] Data are not available for the number of IN naloxone kits purchased by first responder agencies and is not included in this analysis.

On the "Settings" page of the accompanying tool, kits dispensed in the province of Alberta were used as default values. By adjusting the number of kits distributed and observed reversals, this input can be customized to match use by any first responder agency. Observed kit use is input up to period "15", with future use predicted beyond this point.

To estimate the number of kits distributed, a logarithmic curve was fit to the number of kits distributed in past quarters and extrapolated. On average, this results in a 6.3% increase per year over the time horizon considered, although the rate of increase in kit distribution diminishes over time. In the accompanying tool, future distribution of naloxone kits is predicted with a logarithmic curve, with instructions to modify predictions by the user.

9.3.2 *Scenarios*

Three scenarios are considered for the costs associated with IN and IM naloxone for community-based naloxone programs in Alberta. The scenarios demonstrate costs associated with different technology mixes, costs of naloxone kits, the number of kits dispensed, and naloxone shelf life.

9.3.2.1 Scenario 1: Status Quo

Compared to base case predictions of use, strategies of low and high increases in kits dispensed are considered. The low strategy considers a 20% reduction from the estimated kits in the base case, while the high change strategy estimates a 20% increase. The user is able to select different technology mixes to examine their impacts on costs.

9.3.2.2 Scenario 2: Proportion of IN and IM Naloxone

This scenario considers various technology mixes of IN and IM naloxone, with modifiable subsidies for IN naloxone. As the amount of IN naloxone currently distributed is unknown, strategies examined are: 20% IN and 80% IM, 50% IN and 50% IM, and 80% IN and 20% IM administration routes. The user is able to modify the technology mix and the proportion of IN costs subsidized by the public health care payer. This scenario is aligned with current practice where Alberta Health subsidizes police services for IN naloxone kits up to the price of IM kits.[18]

9.3.2.3 Scenario 3: Extended Shelf-Life

In this scenario, costs of wastage due to expiration are explored. Specifically, extending the shelf-life of naloxone from two years to three years is considered. Because Alberta Health subsidizes IN naloxone to the same cost as IM naloxone, results for IM naloxone only are shown. The user is encouraged to adjust these assumptions in the accompanying spreadsheet. A 2019 study found no significant degradation of naloxone in several years past its expiration, in one instance retaining 94% of the labeled concentration 27.5 years after expiration.[91] The United States Food & Drug Administration (FDA) approved extending the shelf-life of NARCAN® intranasal naloxone from 24-months to 36-months, this extension includes previously released products.[92] As such, this scenario examines the budget impact of extending the current 2 year shelf life to 3-years. The estimated number of kits in circulation is provided, alongside the cost to

replace all expired doses. This is a function of reversals, kits distributed in each quarter, and expiring kits. The cost to replace expiring doses is presented alongside the budget impact.

9.3.3 Costs

This analysis uses cost inputs as described in Section 8. Costs of IM naloxone are by kit, which contains three doses of 0.4 mg/mL naloxone. The cost per IM kit is $32.00. For IN naloxone kits, the cost is calculated with two doses of 4 mg/ 0.1mL naloxone, resulting in a cost per kit of $84.00 (Table 14). Community pharmacies dispense the most community-based naloxone kits of registered sites, accounting for 34.4% of kits dispensed in the AHS naloxone program.[50] A dispensation fee of $12.30 is charged for kits distributed by community pharmacies.[93] It was assumed that for kits not distributed by community pharmacies, there would be no dispensation fee. Therefore, it is estimated that each kit dispensed is expected to cost an additional $4.23 in pharmacy fees.

All costs are presented in 2020 Canadian dollars, with no discounting applied. This approach is consistent with budget impact analysis best practice guidelines.[94] As the costs of naloxone kits are variable based on quantity ordered and negotiations with suppliers. The user is encouraged to modify the costs in the accompanying spreadsheet. The base case in all scenarios assumes the mean cost per naloxone kit is the low value provided by Alberta Health as shown in Table 14.[53]

Table 14. Budget Impact Cost Inputs per Naloxone Kit

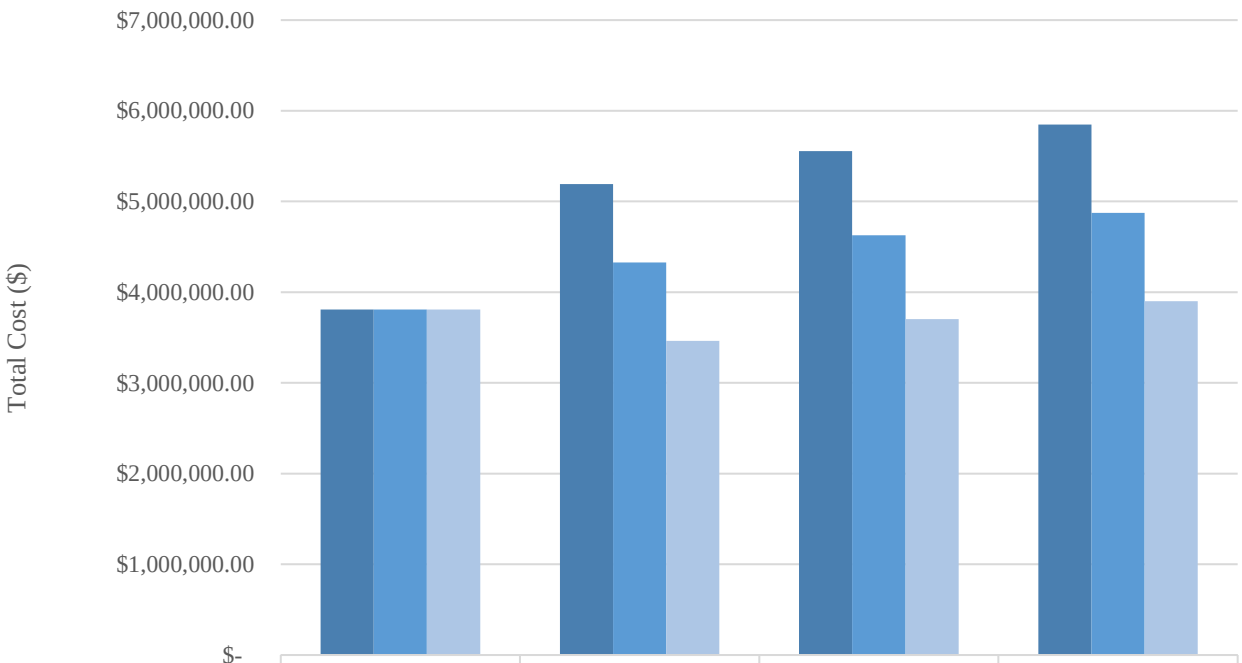
Parameter	Low	High
Intranasal	$84.00	$127.40
Intramuscular	$32.00	$36.00

9.4 Results

9.4.1 Base Case Analysis

In the base case analysis, 486,848 naloxone kits are estimated to be dispensed over 3 years. Costs of the naloxone kits over three years to the province are $17,639,075 (Figure 23). If use is increased by 20% per year above the base line increase, representing high use, the estimated budget impact over three years is $20,405,281; and if use is decreased by 20%, representing low

use, the estimated budget impact over three years is $14,872,869. In this scenario it was assumed that only IM naloxone kits would be dispensed. However, since the province currently subsidizes IN kits up to the same cost as IM, the estimated budget impact for IN kits is the same.

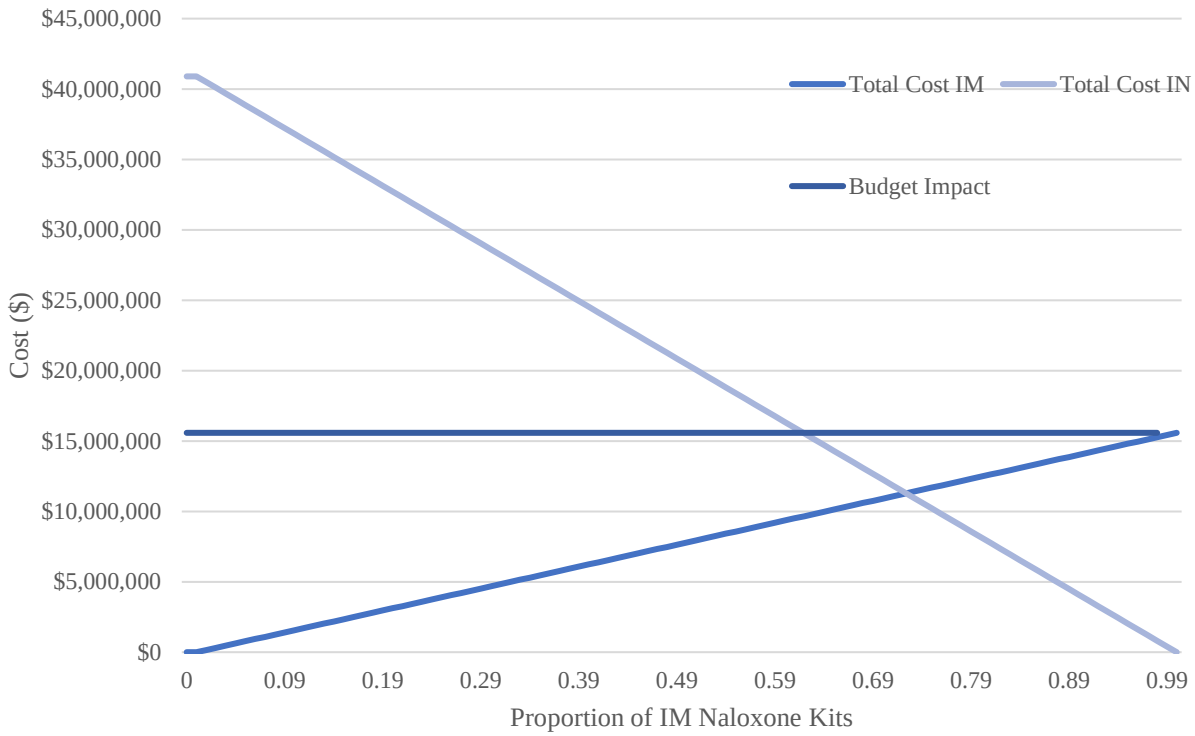


	2020	2021	2022	2023
High use (20% increase)	$3,808,044.04	$5,193,572.46	$5,554,019.28	$5,849,645.36
Base case	$3,808,044.04	$4,327,977.05	$4,628,349.40	$4,874,704.47
Low use (20% decrease)	$3,808,044.04	$3,462,381.64	$3,702,679.52	$3,899,763.57

Figure 23. Estimated Cost per Year for Naloxone Kits

9.4.2 Technology Mix Scenario

In this scenario, the proportion of naloxone kits by each route of administration is varied between zero and one. When the province subsidizes IN naloxone to the same price as IM naloxone, 38.1% of the cost per kit is covered. Assuming the same use as was considered in the status quo scenario base case, the budget impact to the province is consistent at $17,639,075 over 3 years, which includes $2,059,950 in pharmacist dispensing fees. Pharmacist dispensing fees are not affected by the technology mix and are consistent throughout this scenario. However, total costs increase as the proportion if IN naloxone kits increases relative to IM naloxone kits (Figure 24). If all naloxone kits distributed are IN, total costs for naloxone are $42,955,153; and if all naloxone kits distributed are IM, total costs are $17,639,075.



Note: proportion of IN naloxone kits distributed calculated as one minus proportion of IM naloxone kits.

Figure 24. Total Cost for Each Route of Administration as Proportion of IM Naloxone Kits Increases

If 20% of naloxone kits are IM, then the total cost is $37,891,938. Of this value, costs of IM naloxone are $3,115,825, and the costs of IN naloxone are $32,716,163. If 50% of naloxone kits are IM, then the total cost over 3 years is $30,297,114. Of this value, costs of IM naloxone are $7,789,563, and the costs of IN naloxone are $20,447,602. And if 80% of naloxone kits distributed are IM, then the total cost is $$22,702,291, of which $12,463,300 is attributed to IM naloxone and $8,179,041 is attributed to IN naloxone. Because the province subsidizes IN kits up to the same cost as IM, the estimated budget impact is the same regardless of kit distribution. Distribution of IN naloxone kits results in additional costs borne by municipalities and organizations that choose to provide this type of naloxone kit.

Table 15. Costs by Proportion of Naloxone Kits Distributed for Each Administration Route

Proportion IM vs IN	Description	2020 Cost	2021 Cost	2022 Cost	2023 Cost	3-Year Total Cost
80% IM with 20% IN	Cost IM naloxone	$2,690,662	$3,058,033	$3,270,269	$3,444,336	$12,463,300
	Cost IN naloxone	$1,765,747	$2,006,834	$2,146,114	$2,260,346	$8,179,041
	Total Cost	$4,901,126	$5,570,303	$5,956,896	$6,273,966	$22,702,291
	Estimated budget impact	$3,808,044	$4,327,977	$4,628,349	$4,874,704	$17,639,075
50% IM with 50% IN	Cost IM naloxone	$1,681,664	$1,911,271	$2,043,918	$2,152,710	$7,789,563
	Cost IN naloxone	$4,414,368	$5,017,086	$5,365,284	$5,650,864	$20,447,602
	Total Cost	$6,540,748	$7,433,792	$7,949,716	$8,372,858	$30,297,114
	Estimated budget impact	$3,808,044	$4,327,977	$4,628,349	$4,874,704	$17,639,075
20% IM with 80% IN	Cost IM naloxone	$672,666	$764,508	$817,567	$861,084	$3,115,825
	Cost IN naloxone	$7,062,989	$8,027,337	$8,584,454	$9,041,383	$32,716,163
	Total Cost	$8,180,370	$9,297,281	$9,942,535	$10,471,751	$37,891,938
	Estimated budget impact	$3,808,044	$4,327,977	$4,628,349	$4,874,704	$17,639,075

9.4.3 Expiry Date Naloxone Scenario

In this scenario, the impact of expiring kits is considered explicitly; whereas other scenarios only consider the cost for the number of naloxone kits distributed Figure 25 displays the estimated kits in circulation for the total number of kits distributed – with kits in circulation affected by expiration of previously distributed kits and those used for opioid reversal.

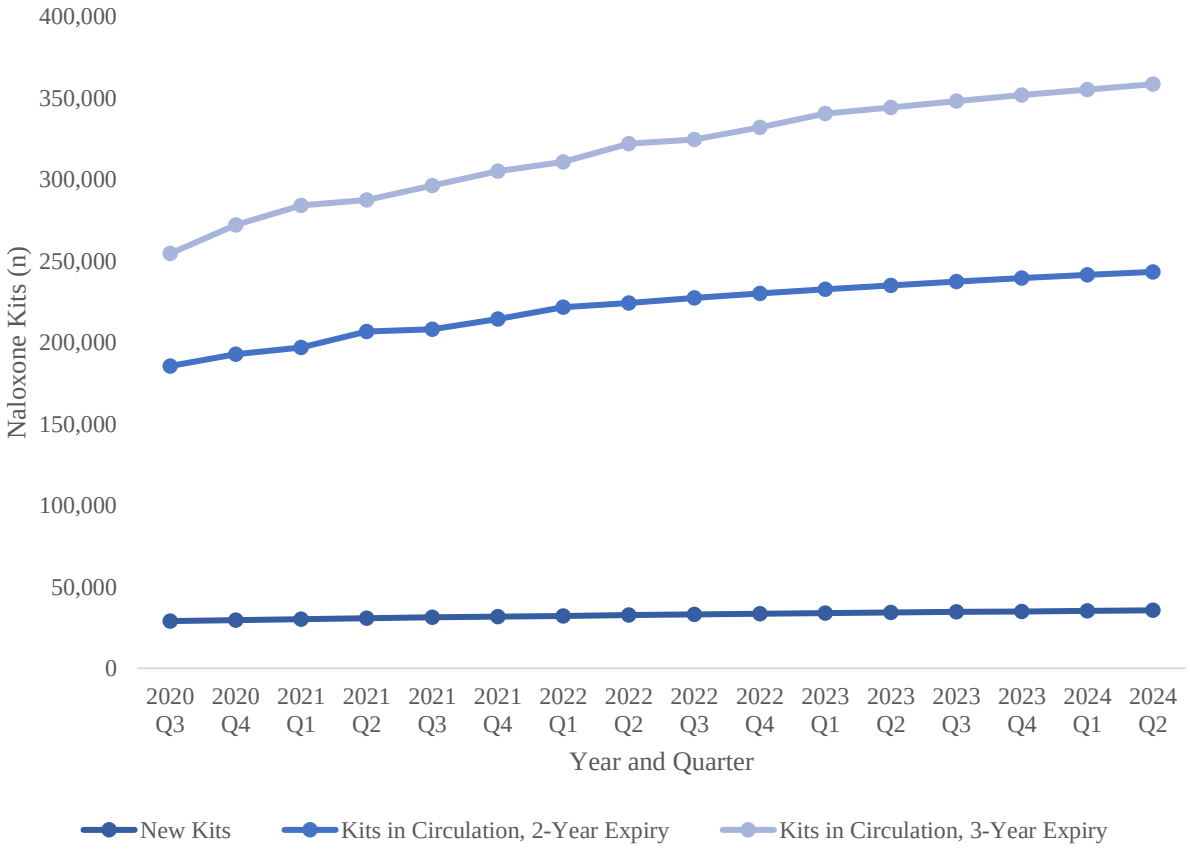


Figure 25. Estimated Kits Distributed and Kits in Circulation by Expiry Date

With a 2-year expiry date, it is expected that there would be a total of 345,495 kits that expire over the 3-year time horizon. The total cost to replace these kits would be $10,885,279. If the expiration date on each kit were pushed back another year, giving a 3-year expiry date, 243,735 naloxone kits would expire within the 3-year time horizon. Costs to the province to replace the expired naloxone kits would be $7,331,362 (

Table 16). In addition to greater numbers of naloxone kits in circulation, a 3-year shelf life would decrease the value of the kits discarded due to expiry by $3,553,917.

Table 16. Estimated Kits in Circulation, Kits Expiring, and Cost to Replace Expired Kits

Year	Quarter	2-Year Expiry			3-Year Expiry		
		Kits in Circulation	Kits Expiring	Cost to Replace Expired Kits	Kits in Circulation	Kits Expiring	Cost to Replace Expired Kits
0	2019 Q3	157,270	8,505	$241,916	173,058	-	*
	2019 Q4	170,024	9,522	$278,256	195,334	-	*
	2020 Q1	176,271	15,551	$509,954	212,520	-	$113,621
	2020 Q2	178,406	24,468	$805,854	236,452	-	$16,123
1	2020 Q3	185,528	19,456	$617,912	254,525	8,505	$221,144
	2020 Q4	192,797	19,788	$625,072	272,060	9,522	$253,123
	2021 Q1	196,935	23,361	$749,658	284,008	15,551	$466,693
	2021 Q2	206,775	18,069	$553,055	287,449	24,468	$784,898
2	2021 Q3	208,009	27,055	$873,760	296,282	19,456	$598,439
	2021 Q4	214,375	22,276	$695,743	305,136	19,788	$605,600
	2022 Q1	221,549	21,798	$673,557	310,747	23,361	$730,186
	2022 Q2	224,227	26,603	$842,780	321,959	18,069	$533,583
3	2022 Q3	227,218	26,578	$836,990	324,472	27,055	$854,288
	2022 Q4	230,000	27,057	$849,497	332,036	22,276	$676,271
	2023 Q1	232,594	27,499	$860,656	340,331	21,798	$654,085
	2023 Q2	235,017	27,909	$870,620	344,060	26,603	$823,308
Total:			**345,495**	**$10,885,279**	**Total:**	**243,735**	**$7,331,362**

*Because no data were available for naloxone kits distributed in 2016 that would expire in Q3 and Q4 in 2019, no estimate of cost to replace to expired kits was generated.

9.5 Conclusions

In all scenarios considered, the estimated budget impact to the province to distribute naloxone kits over 3 years is approximately $19 million. Scenario one demonstrates how costs to the province increase as the number of naloxone kits distributed increases. In scenario two, we see that as the proportion of IN kits distributed increases, the total costs for naloxone increases. Although these costs are not borne by Alberta Health, they would be paid for by the organizations that are delivering and using the naloxone. Distribution and use of IN naloxone

kits results in additional costs, which must ultimately be paid for by Albertans. In the third scenario, costs of expiring naloxone kits are explored. Many of the kits distributed will expire, rather than be used to treat patients. Extending the shelf life of naloxone kits, which was demonstrated to impact efficacy only minimally, would result in greater numbers of naloxone kits in circulation relative to the number distributed. Costs of the expired doses would also decrease. The user is encouraged to adjust base case values used in the accompanying tool to reflect the local context or more accurate data as it becomes available. The results presented in this budget impact analysis are intended to highlight relationships between variables; and the user is encouraged to interpret values of results cautiously.

Regardless of the method of administration, this budget impact analysis shows the significant impact of wastage on costs of naloxone kit distribution. Many of the kits that are distributed are unlikely to be used. Based on distribution of kits and number of reversals reported between 2017 and 2020, there are an average of 14.7 kits distributed per reversal reported. Due to the high variability in number of kits distributed, kits per opioid reversal was not predicted into the future. Without targeted interventions to improve distribution to match use, the cost of the naloxone that goes to waste could be altered by increasing the shelf-life or reducing the cost per kit.

The primary limitation to this budget impact analysis is the lack of administrative data regarding current use. Beyond the number of kits distributed across the province, little is known about the characteristics of the bystanders and first responders that are using naloxone kits. Use of naloxone administered for opioid overdose is likely underreported, with positive effects of naloxone distribution also under-represented. Additional geographic data regarding location of naloxone kit administration and distribution would allow evaluation of cost-effectiveness of distribution plans, which could be used to reduce the costs of expired doses. Communication with other government ministries and standardized reporting that quantifies the amounts of naloxone administered by route of various non-medical first responders, such as fire fighters, law enforcement and corrections officers, and shelter support staff would improve the accuracy of budget impact estimates. Depending on the perspective of the user of the accompanying spreadsheet, inclusion of training costs may be worth considering in future analyses. For this

analysis however, costs were considered from the perspective of Alberta Health, and were therefore not included.

It is recognized that Indigenous peoples living in Alberta are disproportionately impacted by the harms related to opioid use. In April 2018, IN naloxone was listed as an open benefit and made available with no out-of-pocket costs and without a prescription to status First Nations and Inuit that are covered by the Non-Insured Health Benefits (NIHB) program.[95] This program is administered federally by Indigenous Services Canada. Federal programs that increase the availability of naloxone to First Nations and Inuit in Alberta that were not considered in this analysis.

The cost-effectiveness analysis in Section 8 suggested that IM naloxone dominated IN in the base case analysis. Had the distribution pattern been considered in the economic evaluation, it is likely that the cost difference between the two strategies would increase. At 14.7 kits per reversal, costs of IM naloxone used per overdose (assume 100% willingness to use) would be $533, compared to costs of IN naloxone used per overdose of $1,297. Making sure that the administration route for naloxone is the most cost-effective is an important part of Alberta's response to the opioid crisis. Clearly though, the choice to supply IM or IN naloxone is only one variable in a complex response, that depends on other choices, such as the distribution strategy, and inclusion of training costs for first responders.

10 Report Conclusions

This report presents the findings and conclusions of a provincial health technology assessment (HTA) on intranasal (IN) naloxone. The following evidence was considered: a systematic review of clinical effectiveness of naloxone administration methods, a systematic review of patient and care provider perspectives, a cost-effectiveness analysis comparing IN and intramuscular (IM) naloxone, and a budget impact analysis.

The systematic review of clinical effectiveness identified seven studies. Meta-analyses did not find statistically significant differences in most clinical outcomes between IN and non-IN naloxone. However, a meta-analysis of the evidence found that individuals receiving IN naloxone were significantly more likely to require supplemental naloxone (additional dose of naloxone due to lack of effectiveness of the initial dose) than those receiving it intramuscularly or intravenously. IN naloxone was found to result in statistically significantly longer clinical response time (outcome measure not defined by the authors) and lower post-naloxone respiratory rate than IV naloxone, but there were no differences between the two with respect to change in respiratory rate from baseline. Lastly, IN naloxone was not significantly different from IM naloxone with respect to time to respiratory response or adverse events (e.g., agitation, headache, nausea, and vomiting). The quality of the included evidence was generally judged to be either of some concern or of moderate risk of bias.

The systematic review of patient and care provider perspectives identified eight studies. This literature suggests that IN naloxone appears to be the preferred route of administration for both patients and providers. In the one qualitative study examining patient experiences with IN and IM naloxone, most participants were reported to follow administration instructions for IN naloxone that they received during training, but some reported struggling to assemble their IN naloxone kit (this kit was a multi-step atomizer spray which may not be reflective of the devices currently available on the Canadian market [e.g., NARCAN® single-step spray]). Across the survey/quantitative data studies, IN emerged as the preferential route of administration across both the patient and provider studies. Reasons for this preference included ease of administration, reduced blood-borne viruses risk, eliminating the need to carry needles/syringes, painlessness, vein preservation, and less alarming public use. Across the survey studies

examining IN naloxone training for providers, IN naloxone was reported to be easy to use by almost all participants. Based on the findings of this systematic review, IN naloxone appears to be appropriate for dissemination for public and provider use. However, given the scarcity of the qualitative literature, further research on patient and care provider perspectives in this area is warranted.

In the base case cost-effectiveness analysis examining IN and IM routes of naloxone for suspected opioid overdoses administered by bystanders and first responders, IN had a higher cost and equivalent or lower effectiveness than IM naloxone, and was therefore dominated (ICER: -$807.66/reversal; 95% CI: -$983.80 to -$683.42). The cost-effectiveness of IN compared to IM naloxone was sensitive to bystander and first responder willingness to administer. The lifetime time horizon scenario analysis found that IN naloxone is equivalent to IM naloxone. For both routes of administration, mean costs and QALYs were within the 2% margin of error introduced through probabilistic analysis.

In the budget impact analysis, the following scenarios were considered: 1) status quo, 2) technology mix of IN and IM naloxone, and 3) extending expiration dates from 2 to 3 years. In all three scenarios, IN naloxone was associated with higher costs when compared to IM naloxone. In all scenarios considered, the estimated budget impact to the province to distribute naloxone kits over 3 years is approximately $19 million. Scenario one demonstrates how costs to the province increase as the number of naloxone kits distributed increases. In scenario two, we see that as the proportion of IN kits distributed increases, the total costs for naloxone increases. Although these costs are not borne by Alberta Health, they would be paid for by the organizations that are delivering and using the naloxone. In the third scenario, impacts of extending the shelf life of naloxone kits are explored. This is estimated to increase the number of viable naloxone kits in circulation, at reduced cost to the province. An interactive budget impact analysis tool was developed that could be adapted to accommodate future data regarding naloxone kit distribution.

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Appendix A

Systematic Review of Clinical Effectiveness Search Strategy

MEDLINE (August 11, 2020)

1. 36B82AMQ7N.rn.
2. (nalone or naloxon* or Narcan or Narcanti).tw,kf.
3. (antioplaz or maloxone or mapin or nalone or nalonee or narcon or narycam or naxone or nyxoid or zynox).tw,kf.
4. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw,kf.
5. exp Naloxone/ad [Administration & Dosage]
6. ((narcotic or opiate or opioid) adj3 antagonist*).tw,kf.
7. Narcotic Antagonists/
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Administration, Intranasal/
10. nasal sprays/
11. Administration, Inhalation/
12. "Nebulizers and Vaporizers"/
13. (intranasal* or nasal* or nose or inhal* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw,kf.
14. 9 or 10 or 11 or 12 or 13
15. 8 and 14
16. limit 15 to (english or french)
17. limit 16 to (case reports or editorial or letter)
18. 16 not 17
19. animals/ not humans/
20. 18 not 19

EMBASE (August 9, 2020)

1. 465-65-6.rn.
2. 357-08-4.rn.
3. exp naloxone/ad [Drug Administration]
4. (nalone or naloxon* or narcan or narcanti).tw,kw.
5. (antioplaz or maloxone or mapin or nallosone or nalone or nalonee or narcon or narvcam or naxone or nyxoid or zynox).tw,kw.
6. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw,kw.
7. ((narcotic or opiate or opioid) adj3 antagonist*).tw,kw.
8. narcotic antagonist/
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. intranasal drug administration/
11. inhalational drug administration/

12. nose spray/
13. exp nebulizer/
14. (intranasal* or nasal* or nose or inhal* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw,kw.
15. 10 or 11 or 12 or 13 or 14
16. 9 and 15
17. exp naloxone/na [Intranasal Drug Administration]
18. 16 or 17
19. limit 18 to (english or french)
20. limit 19 to (conference abstract or editorial or letter)
21. 19 not 20
22. case report/
23. 21 not 22
24. animals/ not human/
25. 23 not 24

DARE (August 9, 2020)

1. (nalone or naloxon* or Narcan or Narcanti).tw.
2. (antioplaz or maloxone or mapin or nalone or nalonee or Nalossone or narcon or narvcam or naxone or nyxoid or zynox).tw.
3. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw.
4. ((narcotic or opiate or opioid) adj3 antagonist*).tw.
5. 1 or 2 or 3 or 4
6. (intranasal* or nasal* or nose or inhal* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw.
7. 5 and 6

Cochrane Database Systematic Reviews (August 10, 2020)

1. (nalone or naloxon* or Narcan or Narcanti).tw.
2. (antioplaz or maloxone or mapin or nallosone or nalone or nalonee or narcon or narvcam or naxone or nyxoid or zynox).tw.
3. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw.
4. ((narcotic or opiate or opioid) adj3 antagonist*).tw.
5. 1 or 2 or 3 or 4
6. (intranasal* or nasal* or nose or inhal* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw.
7. 5 and 6

Cochrane CENTRAL Register (August 9, 2020)

1. (nalone or naloxon* or Narcan or Narcanti).tw.

2. (antioplaz or maloxone or mapin or nalone or nalonee or Nalossone or narcon or narvcam or naxone or nyxoid or zynox).tw.
3. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw.
4. exp Naloxone/ad [Administration & Dosage]
5. ((narcotic or opiate or opioid) adj3 antagonist*).tw.
6. Narcotic Antagonists/
7. 1 or 2 or 3 or 4 or 5 or 6
8. Administration, Intranasal/
9. nasal sprays/
10. Administration, Inhalation/
11. "Nebulizers and Vaporizers"/
12. (intranasal* or nasal* or nose or inhal* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13
15. limit 14 to (english or french)
16. animals/ not humans/
17. 15 not 16

CINAHL (August 9, 2020)

1. (MH "Narcotic Antagonists") OR (MH "Naloxone+/AD")
2. TI ((nalone or naloxon* or narcan or narcanti)) OR TI ((antioplaz or maloxone or mapin or nalone or nalonee or narcon or narycam or naxone or nyxoid or zynox)) OR AB ((nalone or naloxon* or narcan or narcanti)) OR AB ((antioplaz or maloxone or mapin or nalone or nalonee or narcon or narycam or naxone or nyxoid or zynox)) OR AB (((narcotic or opiate or opioid) N3 antagonist*))
3. 1 or 2
4. (MH "Administration, Intranasal") OR (MH "Nebulizers and Vaporizers")
5. ((MH "Administration, Intranasal") OR (MH "Nebulizers and Vaporizers")) OR TI ((intranasal* or nasal* or nose or inhal*)) OR AB ((intranasal* or nasal* or nose or inhal*))
6. 4 or 5
7. 3 and 6

Limit to English or French

Appendix B

Systematic Review of Patient and Care Provider Perspectives Search Strategy

CINAHL (August 10, 2020)

1. TI ((nalone or naloxon* or narcan or narcanti)) OR TI ((antioplaz or maloxone or mapin or nalone or nalonee or narcon or narycam or naxone or nyxoid or zynox)) OR AB ((nalone or naloxon* or narcan or narcanti)) OR AB ((antioplaz or maloxone or mapin or nalone or nalonee or narcon or narycam or naxone or nyxoid or zynox))
2. (MH "Drug Administration Routes+") OR (MH "Nebulizers and Vaporizers")
3. TI ((administration route* or drug administration or endotracheal* or inhal* or inject* or intralingual* or intramuscular or intra-muscular or intranasal* or intravenous* or intra-venous* or IV or nasal* or nose or subcutaneous* or sublingual* or submental*)) OR AB ((administration route* or drug administration or endotracheal* or inhal* or inject* or intralingual* or intramuscular or intra-muscular or intranasal* or intravenous* or intra-venous* or IV or nasal* or nose or subcutaneous* or sublingual* or submental*))
4. 2 or 3
5. 1 and 4
6. (MH "Naloxone+/AD")
7. 5 or 6
8. ((MH "Patient Preference") OR (MH "Patient Satisfaction") OR (MH "Consumer Attitudes") OR (MH "Consumer Satisfaction") OR (MH "Patient Attitudes") OR (MH "Caregiver Attitudes") OR (MH "Surveys") OR (MH "Survey Research") OR (MH "Questionnaires+") OR (MH "Interview Guides+") OR (MH "Life Histories") OR (MH "Interviews+") OR (MH "Narratives") OR (MH "Focus Groups") OR (MH "Qualitative Studies+")) OR TI ((focus group* or grounded theor* or interview* or lived experience* or qualitative* or questionnaire* or survey*)) OR AB ((focus group* or grounded theor* or interview* or lived experience* or qualitative* or questionnaire* or survey*)) OR TI ((accepta* or attitude* or choice or perspective* or view or views or satisfaction)) OR AB ((accepta* or attitude* or choice or perspective* or view or views or satisfaction)
9. 7 and 8
10. Limit to English or French

MEDLINE (August 7, 2020)

1. exp Naloxone/ad [Administration & Dosage]
2. 36B82AMQ7N.rn.
3. (nalone or naloxon* or Narcan or Narcanti).tw,kf.
4. (antioplaz or maloxone or mapin or nallosone or nalone or nalonee or narcon or narvcam or naxone or nyxoid or zynox).tw,kf.
5. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw,kf.
6. 2 or 3 or 4 or 5

7. exp Drug Administration Routes/
8. nasal sprays/
9. "Nebulizers and Vaporizers"/
10. (administration route* or drug administration or endotracheal* or inhal* or inject* or intralingual* or intramuscular or intra-muscular or IM or intranasal* or intravenous* or intra-venous* or IV or nasal* or nose or subcutaneous* or sublingual* or submental* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw,kf.
11. 7 or 8 or 9 or 10
12. 6 and 11
13. 1 or 12
14. patient satisfaction/ or patient preference/
15. Consumer Behavior/ or Consumer Satisfaction/ or Patient Acceptance of Health Care/
16. "surveys and questionnaires"/ or health care surveys/
17. exp qualitative research/
18. Interview/ or Narration/
19. exp Interview, Psychological/
20. exp Focus Groups/
21. (focus group* or grounded theor* or interview* or lived experience* or qualitative* or questionnaire* or survey*).tw,kf.
22. (accepta* or attitude* or choice or perspective* or view or views).tw,kf.
23. (preference* not "place preference*").tw,kf.
24. satisfaction.tw,kf.
25. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 23 or 22 or 24
26. 13 and 25
27. limit 26 to (english or french)
28. limit 27 to (case reports or editorial or letter)
29. 27 not 28
30. animals/ not humans/
31. 29 not 30

EMBASE (August 10, 2020)

1. 465-65-6.rn.
2. 357-08-4.rn.
3. (nalone or naloxon* or narcan or narcanti).tw,kw.
4. (antioplaz or maloxone or mapin or nallosone or nalone or nalonee or narcon or narvcam or naxone or nyxoid or zynox).tw,kw.
5. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw,kw.
6. 1 or 2 or 3 or 4 or 5
7. exp drug administration route/
8. nose spray/
9. exp nebulizer/

10. (administration route* or drug administration or endotracheal* or inhal* or inject* or intralingual* or intramuscular or intra-muscular or IM or intranasal* or intravenous* or intra-venous* or IV or nasal* or nose or subcutaneous* or sublingual* or submental* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw,kw.
11. 7 or 8 or 9 or 10
12. 6 and 11
13. exp naloxone/ei, ih, ia, ar, ce, cv, ci, dl, du, ig, ly, im, na, io, os, ip, pl, sp, tl, tr, iv, ve, vi, cj, sc, li, tp, td [Epidural Drug Administration, Inhalational Drug Administration, Intraarterial Drug Administration, Intraarticular Drug Administration, Intracerebral Drug Administration, Intracerebroventricular Drug Administration, Intracisternal Drug Administration, Intradermal Drug Administration, Intraduodenal Drug Administration, Intragastric Drug Administration, Intralymphatic Drug Administration, Intramuscular Drug Administration, Intranasal Drug Administration, Intraocular Drug Administration, Intraosseous Drug Administration, Intraperitoneal Drug Administration, Intrapleural Drug Administration, Intraspinal Drug Administration, Intrathecal Drug Administration, Intratracheal Drug Administration, Intravenous Drug Administration, Intravesical Drug Administration, Intravitreal Drug Administration, Subconjunctival Drug Administration, Subcutaneous Drug Administration, Sublingual Drug Administration, Topical Drug Administration, Transdermal Drug Administration]
14. 12 or 13
15. limit 14 to (english or french)
16. limit 15 to (conference abstract or editorial or letter)
17. 15 not 16
18. case report/
19. 17 not 18
20. animals/ not human/
21. 19 not 20
22. patient satisfaction/
23. patient attitude/ or patient preference/
24. consumer attitude/
25. health survey/
26. questionnaire/ or open ended questionnaire/ or structured questionnaire/
27. exp interview/
28. exp qualitative research/
29. grounded theory/
30. (focus group* or grounded theor* or interview* or lived experience* or qualitative* or questionnaire* or survey*).tw,kw.
31. (accepta* or attitude* or choice or perspective* or view or views).tw,kw.
32. (preference* not "place preference*").tw,kw.
33. satisfaction.tw,kw.
34. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 21 and 34

Cochrane Database of Systematic Reviews (August 10, 2020)

1. (nalone or naloxon* or Narcan or Narcanti).tw.
2. (antioplaz or maloxone or mapin or nallosone or nalone or nalonee or narcon or narvcam or naxone or nyxoid or zynox).tw.
3. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw.
4. 1 or 2 or 3
5. (administration route* or drug administration or endotracheal* or inhal* or inject* or intralingual* or intramuscular or intra-muscular or IM or intranasal* or intravenous* or intra-venous* or IV or nasal* or nose or subcutaneous* or sublingual* or submental* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw.
6. 4 and 5
7. (focus group* or grounded theor* or interview* or lived experience* or qualitative* or questionnaire* or survey*).tw.
8. (accepta* or attitude* or choice or perspective* or view or views).tw.
9. (preference* not "place preference*").tw.
10. satisfaction.tw.
11. 7 or 9 or 8 or 10
12. 6 and 11

Cochrane CENTRAL Register (August 10, 2020)

1. exp Naloxone/ad [Administration & Dosage]
2. (nalone or naloxon* or Narcan or Narcanti).tw.
3. (antioplaz or maloxone or mapin or nallosone or nalone or nalonee or narcon or narvcam or naxone or nyxoid or zynox).tw.
4. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw.
5. 2 or 3 or 4
6. exp Drug Administration Routes/
7. nasal sprays/
8. "Nebulizers and Vaporizers"/
9. (administration route* or drug administration or endotracheal* or inhal* or inject* or intralingual* or intramuscular or intra-muscular or IM or intranasal* or intravenous* or intra-venous* or IV or nasal* or nose or subcutaneous* or sublingual* or submental* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw.
10. 6 or 7 or 8 or 9
11. 5 and 10
12. 1 or 11
13. patient satisfaction/ or patient preference/
14. Consumer Behavior/ or Consumer Satisfaction/ or Patient Acceptance of Health Care/
15. "surveys and questionnaires"/ or health care surveys/
16. exp qualitative research/
17. Interview/ or Narration/

18. exp Interview, Psychological/
19. exp Focus Groups/
20. (focus group* or grounded theor* or interview* or lived experience* or qualitative* or questionnaire* or survey*).tw.
21. (accepta* or attitude* or choice or perspective* or view or views).tw.
22. (preference* not "place preference*").tw.
23. satisfaction.tw.
24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 22 or 21 or 23
25. 12 and 24
26. limit 25 to (english or french)
27. animals/ not humans/
28. 26 not 27

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1. (nalone or naloxon* or narcan or narcanti).tw.
2. (antioplaz or maloxone or mapin or nallosone or nalone or nalonee or narcon or narvcam or naxone or nyxoid or zynox).tw.
3. (MRZ-2593 or MRZ2593 or MRZ 2593Br).tw.
4. exp Naloxone/
5. 1 or 2 or 3 or 4
6. exp drug administration methods/
7. (administration route* or drug administration or endotracheal* or inhal* or inject* or intralingual* or intramuscular or intra-muscular or IM or intranasal* or intravenous* or intra-venous* or IV or nasal* or nose or subcutaneous* or sublingual* or submental* or transnasal* or transmucosal* or atomi?e* or nebulize*).tw.
8. 6 or 7
9. 5 and 8
10. client attitudes/ or client satisfaction/
11. consumer satisfaction/ or consumer surveys/
12. Consumer Attitudes/
13. exp surveys/
14. interviews/ or focus group interview/ or exp psychodiagnostic interview/ or semi-structured interview/
15. parent report/ or peer report/ or self-report/
16. exp qualitative methods/
17. (focus group* or grounded theor* or interview* or lived experience* or qualitative* or questionnaire* or survey*).tw.
18. (accepta* or attitude* or choice or perspective* or view or views).tw.
19. (preference* not "place preference*").tw.
20. satisfaction.tw.
21. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 9 and 21

23. animal/ not human/
24. 22 not 23
25. limit 24 to (english or french)
26. limit 25 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract" or "0500 electronic collection")
27. 25 not 26

List of Studies Excluded in Systematic Review of Patient and Care Provider Perspectives

Table B1. List of Studies Excluded in Systematic Review of Patient and Care Provider Perspectives

Author (Year)	Reason for Exclusion
Avetian (2018)[96]	Not patient or care provider perspectives
Bartlett (2011)[97]	Doesn't report on nasal naloxone administration
Gatewood (2016)[98]	Doesn't report on nasal naloxone administration
Holland (2019)[99]	Doesn't report on nasal naloxone administration
Lenglard (2019)[100]	Not patient or care provider perspectives
Neale (2015)[101]	Doesn't report on nasal naloxone administration
Parkin (2020)[102]	Doesn't report on nasal naloxone administration