Community management of opioid overdose

World Health Organization

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CONTENT

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GLOSSARY OF TERMS USED IN THESE GUIDELINES

abstinence

Refraining from alcohol or drug use. The term "abstinence" should not be confused with the term "abstinence syndrome", which refers to a withdrawal syndrome.

agonist

A substance that acts at a neuronal receptor to produce effects similar to those of a reference drug; for example, heroin is a morphine-like agonist at opioid receptors.

antagonist

A substance that counteracts the effects of another agent. Pharmacologically, an antagonist interacts with a receptor to inhibit the action of agents (agonists) that produce specific physiological or behavioural effects mediated by that receptor.

delirium

An acute organic cerebral syndrome characterized by concurrent disturbances of consciousness, attention, perception, orientation, thinking, memory, psychomotor behaviour, emotion, and the sleep-wake cycle. Duration is variable from a few hours to a few weeks and the degree of severity ranges from mild to very severe. An alcohol-induced withdrawal syndrome with delirium is known as delirium tremens.

dependence

A cluster of physiological, behavioural and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol or tobacco.

depressant

Any agent that suppresses, inhibits, or decreases some aspects of central nervous system (CNS) activity. The main classes of CNS depressants are the sedatives/hypnotics (alcohol, barbiturates, benzodiazepines), opioids, and neuroleptics. Anticonvulsants are sometimes included in the depressant group because of their inhibitory action on abnormal neural activity. Disorders related to depressant use are classified as psychoactive-substance use disorders in ICD-10 in categories F10 (for alcohol), F11 (for opioids), and F13 (for sedatives or hypnotics). *See also:* opioid; sedative/hypnotic.

detoxification

Also referred to as managed withdrawal or supported withdrawal, detoxification describes supported cessation of a psychoactive substance.

illicit drug

A psychoactive substance, the production, sale, or use of which is prohibited. Strictly speaking, it is not the drug that is illicit, but its production, sale, or use in particular circumstances in a given jurisdiction. "Illicit drug market", a more exact term, refers to the production, distribution and sale of any drug outside legally-sanctioned channels.

intoxication

A condition that follows the administration or consumption of a psychoactive substance causing disturbances in the level of consciousness, cognition, perception, judgement, affect or behaviour, or other psychophysiological functions and responses.

multiple drug use

The use of more than one drug or type of drug by an individual, at the same time or sequentially, usually with the intention of enhancing, potentiating or counteracting the effects of another drug. The term is also used more loosely to include the unconnected use of two or more drugs by the same person.

naloxone

An opioid-receptor blocker that antagonizes the actions of opioid drugs. It reverses the features of opiate intoxication and is prescribed for the treatment of overdose with this group of drugs. *See also:* antagonist.

opiate

One of a group of alkaloids derived from the opium poppy (*Papaver somniferum*) with the ability to induce analgesia, euphoria and, in higher doses, stupor, coma and respiratory depression. The term opiate excludes synthetic opioids. *See also:* opioid.

opioid

A generic term applied to alkaloids from the opium poppy (*Papaver somniferum*), their synthetic analogues and compounds synthesized in the body, which interact with the same specific receptors in the brain, have the capacity to relieve pain and produce a sense of well-being (euphoria). The opium alkaloids and their synthetic analogues also cause stupor, coma and respiratory depression in high doses.

opioid maintenance treatment

Also referred to as opioid agonist maintenance treatment or opioid substitution treatment. Examples of opioid maintenance therapies are methadone and buprenorphine maintenance treatment. Maintenance treatment can last from several months to more than 20 years, and is often accompanied by other treatment (such as psychosocial treatment).

overdose

The use of any drug in such an amount that acute adverse physical or mental effects are produced. Deliberate overdose is a common means of suicide and attempted suicide. In absolute numbers, overdoses of licit drugs are usually more common than those of illicit drugs. Overdose may produce transient or lasting effects, or death. The lethal dose of a particular drug varies with the individual and with circumstances. *See also:* intoxication; poisoning.

poisoning, alcohol or drug

A state of major disturbance of consciousness level, vital functions and behaviour following the administration in excessive dosage (deliberately or accidentally) of a psychoactive substance. In the field of toxicology, the term poisoning is used more broadly to denote a state resulting from the administration of excessive amounts of any pharmacological agent, psychoactive or not. *See also:* overdose; intoxication.

polydrug use/abuse

See multiple drug use.

psychosocial intervention

Any non-pharmacological intervention carried out in a therapeutic context at an individual, family or group level. Psychosocial interventions range from structured, professionally-administered psychological interventions (such as cognitive behaviour therapy or insight-oriented psychotherapy) to non-professional psychological and social interventions (such as self-help groups and non-pharmacological interventions from traditional healers, accommodation, financial support, legal support, employment assistance, information and outreach).

rebound toxicity

The re-emergence of respiratory depression and other features of opioid overdose following the temporary reversal of opioid overdose symptoms with an opioid antagonist such as naloxone.

relapse

A return to drinking or other drug use after a period of abstinence, often accompanied by reinstatement of dependence symptoms. Some distinguish between relapse and lapse ("slip"), with the latter denoting an isolated occasion of alcohol or drug use.

sedative/hypnotics

Central nervous system depressants that relieve anxiety and induce calmness and sleep. Several such drugs also induce amnesia and muscle relaxation and/or have anticonvulsant properties. Major classes of sedatives/hypnotics include alcohol, the benzodiazepines and the barbiturates.

substance use disorders

This concept includes both the dependence syndrome and the harmful use of psychoactive substances such as alcohol, cannabis, amphetamine-type stimulants (ATS), cocaine, opioids and benzodiazepines.

tolerance

A decrease in response to a drug dose that occurs with continued use. Increased doses of alcohol or other drugs are required to achieve the effects originally produced by lower doses. Both physiological and psychosocial factors may contribute to the development of tolerance, which may be physical, behavioural or psychological.

withdrawal syndrome

Also known as abstinence syndrome, withdrawal reaction, or withdrawal state. A group of symptoms of variable clustering and degree of severity that occur on cessation or reduction of the use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period or in high doses (ICD-10 code F1x.3). The onset and course of a withdrawal syndrome are time limited and relate to the type of substance and dose being taken immediately before cessation or reduction of use. Typically, the features of a withdrawal syndrome are the opposite of acute intoxication.

ACRONYMS & ABBREVIATIONS

ABC	airway, breathing, and circulation
aRR	adjusted relative risk
AIDS	acquired immunodeficiency syndrome
AMA	against medical advice
ART	anti-retroviral treatment
BBV	blood borne virus
BLS	basic life support
CI	confidence interval
CND	Commission on Narcotic Drugs
COCPR	chest compression only cardiopulmonary resuscitation
CNS	central nervous system
CPR	cardiopulmonary resuscitation
CPS	controlled prospective study
ECOSOC	United Nations Economic and Social Council
EMS	emergency medical services
GCS	Glascow Coma Scale
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICD-10	International Classification of Diseases, 10th edition
IM	intramuscular
IN	intranasal
IQR	inter-quartile range
IV	intravenous
OD	overdose
OR	odds ratio
PICO	population, intervention, comparison, outcome
PWID	people who inject drugs
PWUD	people who use drugs
RevMAN	Review Manager
RR	relative risk *or* risk ratio
RCT	randomized controlled trial
SC	subcutaneous
SMD	standardized mean difference
TB	tuberculosis
UNODC	United Nations Office on Drugs and Crime
WHO	World Health Organization
OR	odds ratio

EXECUTIVE SUMMARY

Opioids are potent respiratory depressants, and overdose is a leading cause of death among people who use them. Worldwide, an estimated 69 000 people die from opioid overdose each year. The number of opioid overdoses has risen in recent years, in part due to the increased use of opioids in the management of chronic pain. In 2010, an estimated 16 651 people died from an overdose of prescription opioids in the United States of America alone.

Opioid overdose is treatable with naloxone, an opioid antagonist which rapidly reverses the effects of opioids. Death does not usually occur immediately, and in the majority of cases, overdoses are witnessed by a family member, peer or someone whose work brings them into contact with people who use opioids. Increased access to naloxone for people likely to witness an overdose could significantly reduce the high numbers of opioid overdose deaths. In recent years, a number of programmes around the world have shown that it is feasible to provide naloxone to people likely to witness an opioid overdose, in combination with training on the use of naloxone and the resuscitation of people experiencing opioid overdose, prompting calls for the widespread adoption of this approach. In 2012, the United Nations Economic and Social Council (ECOSOC) called upon the World Health Organization (WHO), in collaboration with the United Nations Office on Drugs and Crime (UNODC) to provide advice and guidance, based on scientific evidence, on preventing mortality from drug overdose, in particular opioid overdose.

While community management of opioid overdose with naloxone is expected to reduce the proportion of witnessed opioid overdoses which result in death, it does not address the underlying causes of opioid overdose. To further reduce the number of deaths due to opioid overdose other measures should be considered, such as:

- monitoring opioid prescribing practices;
- curbing innapropriate opioid prescribing;
- curbing inappropriate over-the-counter sales of opioids;
- increasing the rate of treatment of opioid dependence, including for those dependent on prescription opioids.

Objectives of the guidelines

These guidelines aim to reduce the number of deaths from opioid overdose by providing evidence-based recommendations on the availability of naloxone for people likely to witness an opioid overdose along with advice on the resuscitation and post-resuscitation care of opioid overdose in the community. Specifically, these guidelines seek to:

- increase the availability of naloxone to people likely to witness an opioid overdose in the pre-hospital setting;
- increase the preparedness of people likely to witness an opioid overdose to respond safely and effectively by carrying naloxone and being trained in the management of opioid overdose;
- increase the rate of effective resuscitation and post-resuscitation care by persons witnessing an opioid overdose.

The guidelines aim to meet these objectives by:

- informing health policy-makers of the benefits of increased availability and use of naloxone and effective resuscitation in the pre-hospital setting;
- informing programme managers of the benefits of developing programmes to equip people likely to witness an opioid overdose with naloxone and to train them in managing an opioid overdose;
- informing medical practitioners of the benefits of prescribing naloxone to people at risk of opioid overdose and providing advice on the management of opioid overdose.

How these guidelines were developed

Development of these guidelines began in October 2013 with the identification of the key issues for which advice was needed. The WHO steering group and Guideline Development Group (GDG) were established and appropriate clinical questions were formulated. These were then set in the PICO format (population, intervention, comparator, outcome) and systematic reviews were conducted for each PICO question. The quality of the evidence was then assessed according to GRADE criteria. A narrative evidence synthesis was also provided. A GDG meeting was held in Geneva (19-20 February 2014). Evidence of values and preferences, cost-effectiveness, feasibility and resource use was presented along with the evidence of benefits and harms and the GDG formulated recommendations taking all these domains into consideration.

The strength of the recommendation was set as either:

'strong': meaning that the GDG was confident that the evidence of effect, combined with certainty about the values, preferences, benefits and feasibility, made this a recommendation that should be applied in most circumstances and settings;

or

'conditional': meaning that there was less certainty about the evidence of effect and values, preferences, benefits and feasibility of this recommendation. Thus there may be circumstances or settings in which the recommendation does not apply.

TABLE 1. SUMMARY OF THE RECOMMENDATIONS

No.	Recommendation	Strength of recommendation	Quality of evidence
1	People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.	Strong	Very low
2	Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting and local context.	Conditional	Very low
3	In suspected opioid overdose, first responders should focus on airway management, assisting ventilation and administering naloxone.	Strong	Very low
4	After successful resuscitation following the administration of naloxone, the level of consciousness and breathing of the affected person should be closely observed until full recovery has been achieved.	Strong	Very low

INTRODUCTION

Opioids are potent respiratory depressants, and overdose is a leading cause of death among people who use them. Worldwide, an estimated 69 000 people die from opioid overdose each year *(1)*. Among people who inject drugs, opioid overdose is the second most common cause of mortality after HIV/AIDS *(2)*. A recent rise in opioid-overdose deaths in a number of countries is associated with an increase in the prescribing of opioids for chronic pain *(3–5)*. In 2010, an estimated 16 651 people died from an overdose of prescription opioids in the United States of America alone *(6)*.

Opioid overdose

Opioids depress the respiratory drive and overdose is characterised by apnoea, myosis and stupor. A severely reduced respiration rate results in hypoxaemia, leading to cerebral hypoxia and impaired consciousness. Cardiac arrest is a late complication of opioid overdose and secondary to respiratory arrest and hypoventilation. Prolonged cerebral hypoxia is the mechanism for brain injury and death in opioid overdose, resulting from apnoea or cardiac dysrhythmias and cardiac arrest.

Opioids act at μ, κ and δ-opioid receptors, which are widely distributed throughout the body. Endogenous opioids act tonically on brain-stem-located opioid receptors to modulate respiration in response to hypoxia and hypercapnea *(7)*. These centres are in turn modulated by connections to other structures in the central nervous system (CNS) including the motor cortex, the cerebellum and limbic centres. Administered opioids depress all components of the respiratory drive (the rate and depth of breathing). An effect most pronounced in individuals with chronic cardio-pulmonary and renal disease, whose respiratory responses are diminished. In addition to reducing respiratory drive, opioids reduce upper-airway tone and chest-wall rigidity.

Preventing opioid overdose

While community management of opioid overdose with naloxone is expected to reduce the proportion of witnessed opioid overdoses which result in death, it does not address the underlying causes of opioid overdose. To further reduce the number of deaths due to opioid overdose other measures should be considered *(8)*, such as:

- monitoring opioid prescribing practices;
- curbing innapropriate opioid prescribing;
- curbing inappropriate over-the-counter sales of opioids;
- increasing the rate of treatment of opioid dependence, including for those dependent on prescription opioids.

Who is at risk of an opioid overdose

People dependent on opioids are the group most likely to experience an overdose. The incidence of fatal opioid overdose among opioid-dependent individuals is estimated at 0.65 per 100 person years *(8)*. Non-fatal opioid overdoses are several times more common than fatal ones *(9)*.

A number of risk factors lead to increased likelihood of a fatal opioid overdose. Injecting opioid users are at elevated risk, particularly when first using injection as a route of administration *(10–12)*.

A reduction in tolerance, seen when opioid use is restarted after a period of abstinence, markedly increases the risk of an opioid overdose *(13, 14)*. This commonly occurs during the first few weeks after release from incarceration *(15–17)*, after discharge from inpatient or residential detoxification, or cessation of drug dependence treatment (including treatment with the opioid antagonist naltrexone) *(18–21)*.

People who inject drugs and have HIV infection have an increased risk of overdose but it is unclear if the mechanism is direct or relates to a combination of biological, risk-behavioural and structural factors *(26)*. Liver disease may also impair hepatic opioid metabolism *(27)* and therefore contribute to lowering overdose thresholds among individuals with chronic viral hepatitis, particularly long-standing hepatitis C viral infection *(28)*.

Although people taking prescribed opioids are at lower risk of overdose than people using unprescribed opioids, the high number of people receiving prescribed opioids in many countries mean that they constitute a significant proportion of opioid overdose deaths, if not the majority. Risk factors for overdose in people taking prescribed opioids include higher prescribed dosage, male gender, older age *(29, 30)*, multiple prescriptions (including benzodiazepines) *(31)*, mental health disorders and lower socioeconomic status *(32–34)*. The risk of overdose is significantly higher where the prescribed dose is 100 mg morphine equivalents daily or greater *(29)*.

Who is likely to witness an opioid overdose

Most opioid overdoses occur in private homes *(35)*, and most of these are witnessed *(36–38)*. Close friends, a partner or family members are most likely to witness an opioid overdose *(39, 40)*.

The other key group of individuals likely to witness overdoses are people working with people who use drugs. They include trained health professionals and first responders, such as ambulance, police, fire and drug-treatment workers as well as outreach workers.

Management of opioid overdose

Death in opioid-overdose can be averted by emergency basic life support resuscitation and/or the timely administration of an opioid antagonist such as naloxone.

Naloxone (n-allylnoroxymorphone) has been used in opioid overdose management for over 40 years, with minimal adverse effects beyond the induction of opioid withdrawal symptoms *(42)*. It is a semisynthetic competitive opioid antagonist with a high affinity for the μ opioid receptor. It rapidly displaces most other opioids from opioid receptors, and if given soon enough will reverse all clinical signs of opioid overdose. It can be administered by a variety of routes including intravenously (IV), intramuscularly (IM), subcutaneously (SC) and intranasally (IN). It carries no potential for abuse, although high doses may lead to the development of opioid withdrawal symptoms such as vomiting, muscle cramps and agitation.

Access to naloxone

Access to naloxone is generally limited to health professionals, and in many countries there is limited availability of naloxone even in medical settings, including ambulances.

Naloxone is a prescription medicine in almost all countries, and while it is not usually prescribed to people likely to witness an opioid overdose, at least one country has made naloxone available in pharmacies without prescription.

Why these guidelines were developed

In recent years, several countries in different regions have started distributing naloxone to people likely to witness an opioid overdose, initially in pilot programmes, but now also in some cases state or national policy, demonstrating the feasibility of this approach and prompting calls for widespread adoption of this approach *(43)*.

In 2012, the United Nations Economic and Social Council (ECOSOC) called upon the World Health Organization (WHO), in collaboration with the United Nations Office on Drugs and Crime (UNODC), to provide evidence-based guidance on preventing mortality from drug overdose, in particular opioid overdose *(44)*.

Existing relevant guidelines on related problems and disorders

The table below lists existing WHO guidelines containing recommendations on the use of naloxone for the management of opioid overdose. They recommend using a dose of 0.4 mg naloxone and repeating the dose if necessary, and suggest monitoring the person for four hours after resuscitation. These guidelines also state that it is not necessary to retain people against their will during this period, and that long-acting-opioid overdose should be managed in hospital with assisted ventilation and/or naloxone infusion.

Naloxone is already recommended for use by trained health care providers managing opioid overdose and is included in the WHO Model Lists of Essential Medicines. However, there is currently no guidance on use of naloxone by those who witness an overdose in a non-hospital, community setting. The current guidelines were developed to provide advice on who should be provided with naloxone, on dosage, administration and accompanying actions, particularly cardio-respiratory resuscitation.

TABLE 2. EXISTING RELEVANT WHO GUIDELINES RELATED TO OPIOID OVERDOSE

WHO guidelines	Recommendations
Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (2009) http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf	Contains recommendations on the treatment of opioid dependence, including opioid overdose, but does not address the issue of non-medical availability of naloxone.
MhGAP – Intervention Guide (WHO, 2010) http://www.who.int/mental_health/evidence/mhGAP_intervention_guide/en/ index.html	Contains recommendations on management of opioid overdose and on how to respond to drug-use disorders in general (i.e. after the overdose has resolved).
The ASSIST linked brief intervention for hazardous or harmful substance use (WHO, 2010) http://whqlibdoc.who.int/publications/2010/9789241599399_eng.pdf	Contains recommendations on how to talk to people about their substance use.
IMAI District Clinical Manual: Hospital Care for adolescents and Adults (WHO, 2011) http://www.who.int/hiv/pub/imai/imai2011/en/	Contains recommendations on the management of opioid overdose in the emergency-department setting.

Who should use these guidelines

These guidelines are relevent to health policy-makers and services that care for people at risk of opioid overdose and people likely to witness an opioid overdose in the community setting.

People likely to witness an opioid overdose in the community setting include:

- people at risk of an opioid overdose, their friends and families;
- people whose work brings them into contact with people who overdose (health care workers, police, emergency service workers, people providing accommodation to people who use drugs, peer education and outreach workers).

The following are examples of health service which could provide people likely to witness an opioid overdose with access to naloxone and training in its use:

- drug treatment services
- pain clinics prescribing opioids

- HIV treatment services
- hospital emergency departments
- emergency care services.

Objectives and scope of these guidelines

The objective of these guidelines is to reduce the mortality and morbidity of opioid overdose by improving the pre-hospital management of opioid overdose. Specifically, the guidelines seek to:

- increase the availability of naloxone to people likely to witness an opioid overdose in the pre-hospital setting;
- increase the preparedness of people likely to witness an opioid overdose to respond safely and effectively by carrying naloxone and being trained in the management of opioid overdose;
- increase the rate of effective resuscitation and post-resuscitation care by persons witnessing an opioid overdose.

The guidelines aim to meet these objectives by:

- informing health policy-makers of the benefits of increased availability and use of naloxone and effective resuscitation in the pre-hospital setting;
- informing programme managers of the benefits of developing programmes to equip people likely to witness an opioid overdose with naloxone and to train them in managing an opioid overdose;
- informing medical practitioners of the benefits of prescribing naloxone to people at risk of opioid overdose and providing advice on the management of opioid overdose.

Individuals and partners involved in development of the guidelines

Members of the project's **WHO Steering Group** were drawn from Management of Substance Abuse, HIV, Essential Medicines and Health Products, Injury and Violence Prevention, Global TB Programme, and Service Delivery and Safety teams (see Annex 7 for details).

The project's **Guideline Development Group** (GDG) was made up of content experts from all WHO regions, five of whom were female. A full list of members, their affiliations, expertise and countries is provided in Annex 7. Observers representing people at risk of opioid overdose and other stakeholder groups attended the GDG meeting in Geneva in February 2014, provided comments and technical information but did not participate in formulation of the recommendations. A full list of observers who attended the meeting and their affiliations is available in 'Acknowledgements' on page 5.

The GDG was supported by several consultants, three who performed the systematic reviews and provided all background documentation, and a fourth who advised on WHO guideline development methodology. A GRADE methodologist reviewed the findings of the systematic review and developed the GRADE evidence profile (see Annex 8 for details).

The **External Review Group**, whose members were drawn from people who may be affected by the guidance and people with content expertise, assessed all the evidence profiles and draft recommendations. The systematic reviewers and GDG considered their comments when finalizing the recommendations. A full list of external reviewers, their affiliations, countries, and expertise is provided in Annex 7.

Management of conflicts of interest

All GDG members, external reviewers and consultants completed the WHO Declaration of Interest forms. Several GDG members declared academic and financial interests. These were then reviewed by the secretariat for potential conflicts of interest. Where conflicts of interest were assessed as potentially serious, they were referred to the WHO legal department (see summary in Annex 8). The declared interest of Bob Balster (chair) was determined not to represent a conflict for these guidelines. Two GDG members were assessed to have a serious conflict of interest. Raka Jain's conflict was assessed as serious as she had received funding from Rusan Pharmaceuticals, a manufacturer of naloxone, although it was for work on an unrelated product. John Strang's

conflict was considered serious because his organization had received funding from Martindale, a manufacturer of naloxone, even though the funding was for work on an unrelated product, and because of his current work on a non-injectable formulation of naloxone. Both were excluded from participation in discussions and decisions relating to the use and availability of naloxone. The remaining conflicts of interest were not considered serious and thus all other GDG members were able to participate in all decisions.

How the guidelines were developed

These guidelines were developed in accordance with the WHO Handbook for Guideline Development *(45)*, and the process was overseen by the WHO Guidelines Review Committee. Development of the guidelines began in October 2013 with the establishment of the WHO Steering Group and the Guideline Development Group (GDG) which identified the key questions on which advice was needed. These questions were then formulated in PICO format (population, intervention, comparator, outcome). The GDG selected a list of outcomes for each PICO question and then ranked these by importance on a scale from 1 to 9. A ranking of 7–9 was considered "critical", 4–6 "important" and 1–3 "not important". Only critical and important outcomes were considered.

Systematic evidence search and retrieval

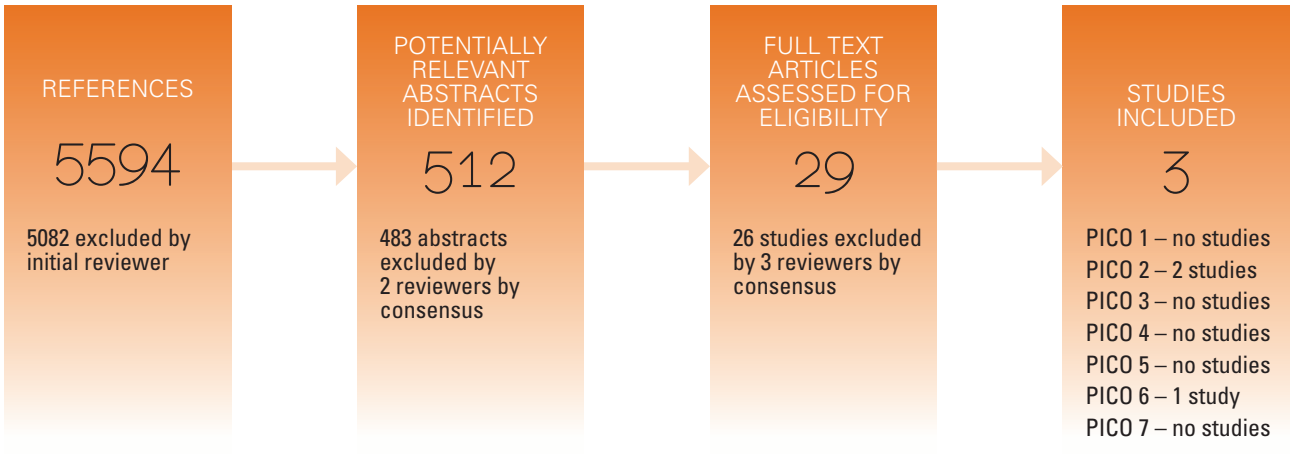
The seven key questions governed the search strategy for the systematic reviews. There was considerable overlap in the areas to be searched, so for efficiency the strategy for searching the medical-literature databases for each of the reviews was combined and the inclusion and exclusion criteria were applied separately by the persons reviewing the results of the database search (see Annex 1 for details of the search strategy).

To obtain reliable estimates of effect for the different PICO questions, it was agreed that eligible studies be limited to randomized controlled trials (RCTs) or controlled prospective studies published in peer-reviewed journals, or presented as abstracts at scientific conferences, between 1 January 1966 and 1 January 2014. The search identified 5597 articles. These were screened by a single researcher, yielding 512 potentially relevant studies. Further screening by two researchers independently (disagreement resolved by discussion) reduced these to 29 relevant studies. Three researchers, including a GRADE methodologist, independently screened and agreed on the final three included studies.

Data analysis was conducted using Review Manager (RevMan) Version 5.2 (The Nordic Cochrane Centre, Copenhagen) and GRADEprofiler (GRADEpro) version 3.6 (the GRADE working group). Where there was no effect size or studies could not be assessed using GRADEpro a narrative summary of the evidence was provided (see summaries in Annexes 2, 3, 4, and 5).

Evidence to recommendations

FIGURE 1. STUDY SELECTION FLOW DIAGRAM



The quality of the evidence retrieved was assessed using GRADE methodology *(46–47)*. GRADE evidence profiles were developed for each key question, summarizing the quality of the evidence, a narrative assessment of benefits versus risks and harms, the estimated values and preferences of those who might be affected by the guidelines, and the costs, resource utilization and feasibility of the proposed interventions. Where necessary, these narrative descriptions also referred to other relevant evidence, not included in the systematic reviews, including one interrupted time-series analysis and 20 case series of programmes that had distributed naloxone (relevant to key questions 1–3), and five case series of opioid overdose recovery after naloxone (relevant to key question 5). The characteristics of these studies and relevant outcomes are presented in Annexes 2–5.

An online survey was conducted by WHO to assess the values and preferences of those affected by the guidelines. This was completed by 661 respondents from 45 countries, including people at risk of opioid overdose, people with family members or friends who have overdosed or are at risk of opioid overdose, and people whose work brings them into contact with people who have experienced overdose and people at risk of overdose. A separate survey of 32 key informants was conducted by a consultant to the Department of HIV/AIDS, as part of a survey on HIV prevention, testing, treatment, harm reduction and community distribution of naloxone (see Annex 6 for a detailed extract from the survey).

With the exception of the values-and-preferences survey and key-informant results, the GRADE profiles were circulated for external review prior to the face-to-face meeting of the GDG.

The guideline development meeting, held in Geneva (19–20 February 2014), was attended by GDG members and observers from organizations working with or representing people who use drugs, relevant professional societies, concerned government health agencies, intergovernmental organizations and WHO collaborating centres. Materials presented included GRADE evidence profiles, evidence summaries and systematic reviews, along with background documentation and findings from the values-and-preferences survey and key-informant interviews.

A GRADE decision table was used to guide the determination of the strength of each recommendation (strong or conditional), based on the quality of the evidence, whether benefits outweighed harms, whether values and preferences of guideline end-users favoured the recommendation, and whether or not the recommendation was feasible and cost-effective (see Annexes 2-5 for the decision tables).

The strength of each recommendation was set as either:

'strong': meaning that the GDG was confident that the evidence of effect, combined with certainty about the values, preferences, benefits and feasibility, made this a recommendation that should be applied in most circumstances and settings;

or

'conditional': meaning that there was less certainty about the evidence of effect and values, preferences, benefits and feasibility of this recommendation. Thus there may be circumstances or settings in which the recommendation does not apply.

At the beginning of the meeting, the GDG agreed that decisions on the strength and wording of recommendations would preferably be reached by consensus – defined as a state where all members of the GDG agree with the wording of recommendations and accompanying comments. It was further agreed that when unanimous agreement could not be achieved, an open vote would be held and decisions carried by a simple majority (more than 50%). In the meeting, the wording of all recommendations was agreed by consensus, and voting was not required.

While discussing the recommendations, the GDG recommended that the scope of the guidelines be limited to pre-hospital care, enabling the guideline to be better targeted to opioid overdose in the community setting. This meant that several of the questions (key question 6 on use of naltrexone and naloxone infusion and key question 7 on the use of flumazenil in the management of mixed opioid and sedative overdose) were no longer within the scope of the guideline and were therefore not discussed further at the meeting.

Peer review process

After the meeting, the draft recommendations and background systematic reviews were circulated to a group of external reviewers (see Annex 7 for details). Revision of the draft recommendations and remarks was made if reviewers identified an issue that had not been considered at the guidelines meeting or proposed changes which improved the clarity of the text without changing the meaning. The revised recommendations were then circulated among the GDG members and proposed changes were accepted if agreed upon by the entire group.

RECOMMENDATIONS

Key question 1 – naloxone distribution (see Annex 2 for details)

Background

Naloxone is a semisynthetic competitive opioid antagonist with highest affinity for the μ-receptor, though it also acts at κ and δ-opioid receptors. It rapidly reverses all clinical signs of opioid overdose when administered. Consequently, timely administration of naloxone during overdose is crucial for reducing mortality associated with opioid overdose. Distribution of naloxone to laypersons may reduce the time taken to give naloxone and thus reduce overdose mortality.

Key question

Should naloxone be distributed to people who are likely to witness an opioid overdose?

Systematic review

Of the 5594 studies screened, none fulfilled the eligibility criteria.

Summary of the evidence

There were no studies that met the inclusion criteria for the review.

Benefits and harms

Although there were no studies that met the criteria for low risk of bias set by the systematic review, there were 20 studies reporting some data on the provision of naloxone to people likely to witness an opioid overdose ("take-home" naloxone), which are summarized in Annex 2. More than 50 000 doses of naloxone have been distributed in the USA alone. Based on this data, the estimated mortality rate in overdoses witnessed by people who have been given naloxone is 1.0% (95% CI 0.83% to 1.21%). Although there was no comparator in these studies, the mortality rate of opioid overdose where community use of naloxone was not available has been estimated at 2–4% *(9)*. These case series estimated the rate of acute opioid withdrawal at 7.6% following naloxone (4.9% to 10.2%), and the only adverse event reported being seizures which occurred in 0.45% of overdose reversals.

An interrupted-time-series analysis found that take-home naloxone was associated with lower overdose death rates (aRR 0.73 [0.57–0.91]) *(48)*.

The GDG judged the risk-benefit profile to be strongly in favour of naloxone distribution, due to its clear potential for saving lives and apparent low risk of significant adverse effects. While training was considered an important and intrinsic component of increased naloxone availability, the GDG cautioned against making it compulsory or institutionalizing it as there were concerns that lack of certified training may be used as a barrier to provision of naloxone. The panel noted that while minor adverse events from naloxone administration (such as vomiting and opioid withdrawal) were not uncommon, serious adverse events were extremely rare.

Values and preferences

Naloxone distribution programmes may assist in the timely treatment of overdose where emergency help is unavailable or unlikely to reach the overdosing person in time *(57, 61, 62)*.

The online values-and-preferences survey (see Annex 6) revealed a strong preference for receiving naloxone and resuscitation after overdose, including from lay first responders unknown to the person who had overdosed. Non-medically trained respondents indicated a high level of willingness to provide naloxone and resuscitation to

strangers who had overdosed. Those able to prescribe medication showed a strong preference for prescribing naloxone to both people at risk of overdose and people likely to witness an overdose. The majority indicated preparedness to carry naloxone with them at all times. Health care workers confirmed that naloxone was often not currently available in medical settings.

Participants in the in-depth interviews were also strongly in favour of wider naloxone availability.

Costs and resource use

The panel judged naloxone distribution and training interventions to be currently cost-effective across a range of economic settings for the treatment of opioid overdose in the community. Approximately 20% of doses distributed in observational studies are reported to be used. Naloxone was used in approximately 70% of the overdoses witnessed by laypersons provided with take-home naloxone *(50–54)*. However, the panel noted that while naloxone is currently affordable, there is a possibility that new formulations targeted for community use will be developed, and that should the price rise considerably this may be a less cost-effective intervention. The panel noted the lack of analyses or modelling studies to guide assessment of the cost-effectiveness of take-home naloxone programmes for people using prescribed opioids.

Feasibility

Naloxone distribution appears feasible in most socioeconomic settings. However, the panel noted that prescription regulations in different jurisdictions may be a barrier to provision of take-home naloxone.

RECOMMENDATION 1 (KEY QUESTION 1)

People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose.

Strength of recommendation: Strong **Quality of evidence: Very low**

REMARKS

- There may be both legal and policy barriers to the access and use of naloxone by lay first responders, which may need to be reviewed in order to implement this recommendation.
- In addition to the use of naloxone, emergency care of suspected opioid overdose should include ventilation support, airway management and management of withdrawal effects (specific emergency-care measures are described in Recommendation 3). While comprehensive training in opioid overdose and resuscitation is desirable, basic training can enable the effective emergency use of naloxone and the lack of more extensive training should not impede its use in the community. There are many training programmes available reflecting local contexts and needs.
- The panel notes that the people at risk of overdose and those likely to witness an overdose may vary according to the local context (see examples in Table 3).
- Access to naloxone implies that the price remains affordable. The GDG made a strong recommendation for the use of naloxone based on current prices but note that this could change if prices rise drastically.

Decision on strength of recommendation: The GDG determined that this recommendation should be strong despite the very low quality evidence due to the life-saving nature of the intervention and the apparent absence of significant harm. The panel also noted that this is a feasible intervention, highly valued by those at risk of opioid overdose and those likely to witness an opioid overdose in the community.

TABLE 3. EXAMPLES OF PEOPLE AT HIGHER RISK OF OVERDOSE AND PEOPLE LIKELY TO WITNESS AN OVERDOSE

People at higher risk of overdose	• people with opioid dependence, in particular those with reduced tolerance (following detoxification, release from incarceration, cessation of treatment) • people who inject opioids • people who use prescription opioids, in particular those on higher doses • people who use opioids in combination with other sedating substances • opioid users with other significant medical conditions (HIV, liver or lung disease, depression) • household members of people in possession of strong opioids
People likely to witness an overdose	• people at risk of an opioid overdose, their friends and families • people whose work brings them into contact with people who overdose (health care workers, police, emergency service workers, people providing accommodation to people who use drugs, peer education and outreach workers)

Key questions 2 and 3 – formulation and dose of naloxone (see Annex 3 for details)

Evidence for key question 2 on naloxone dose and key question 3 on naloxone route of administration were considered together, given the potential for an interaction between dosing and route of administration.

Background

Naloxone, formulated as naloxone hydrochloride, is available in 0.02 mg, 0.4 mg and 1 mg per 1 ml vials, 2 mg/1 ml, 2 mg/2 ml, 2 mg/5 ml prefilled syringes, and a 4 mg/10 ml multi-dose vial. It is currently not under patent and available through generic manufactures. The intravenous (IV) route requires intravenous access. Intramuscular (IM) and subcutaneous (SC) routes do not require IV access, but require a needle. The intranasal (IN) route does not require a needle; typically a syringe containing naloxone (either a prefilled syringe or drawn up from a vial) is attached to a mucosal atomization device which generates a fine mist of naloxone containing solution when the syringe plunger is pressed. To date, there has been no formulation of naloxone registered specifically for IN use.

The naloxone dose needed to achieve reversal of opioid overdose is a function of the dosage of administered opioid, other concurrently administered drugs (particularly sedatives) and a variety of other factors. Given the uncertainties surrounding the dose of opioid taken, and the presence of other drugs, several international guidelines recommend titration of naloxone until clinical reversal is apparent *(63–65)*.

Key question (combined)

What formulation and dosage of naloxone should be used in the initial management of opioid overdose, including by lay responders, in the pre-hospital setting?

Systematic review

Of the 5594 studies screened, two RCTs fulfilled the eligibility criteria *(66, 67)*. Both were field-based RCTs conducted in Victoria, Australia, comparing use of intranasal versus intramuscular naloxone by paramedics in people with suspected opioid overdose in pre-hospital settings.

Evidence to recommendation

Summary of findings

Meta-analysis of the two eligible RCTs found no difference between the administration of intranasal naloxone (initial dose 2 mg) versus intramuscular naloxone (initial dose 2 mg) for opioid overdose. There was no difference in the rates of overdose complications (relative risk (RR) 0.36 [0.01 to 8.65]), overdose morbidity (RR 0.85 [0.71 to 1.03]), opioid withdrawal reaction to naloxone (RR 0.42 [0.1 to 1.65]) or time to opioid reversal (mean difference (MD) 1.05 higher [0.81 lower to 2.91 higher]). There were no deaths in either study. Ease of administration was not estimable.

There were no studies examining IV administration compared to IN or IM naloxone administration.

There were no studies comparing different doses or dosing regimens of naloxone (such as titration versus single dose).

Benefits and harms

The panel judged the efficacy of naloxone in the treatment of opioid overdose to be largely independent of the route of administration. The panel noted that IV administration may not be appropriate for use in the community. The extra time required to achieve intravenous access and administration compared with intramuscular or intranasal administration was also noted. An added benefit of intranasal preparations was that because they do not require a needle, they eliminate the risk of needlestick injury.

The panel noted the evidence from observational studies that initial doses in the range of 0.4 to 2 mg have been used successfully for reversing opioid overdose in the community, and that on occasions, two or more doses were required. The possibility of adverse effects (including prolonged opioid withdrawal and seizures) with the use of naloxone doses higher than 2 mg was considered a potential harm.

Values and preferences

Published surveys have shown a high degree of preparedness by non-medically trained persons to administer naloxone to family members, friends and strangers who have overdosed, with a preference for the intranasal formulation *(68, 69)*. This was confirmed in the online survey conducted for these guidelines. Observers also informed the GDG meeting that people who have overdosed prefer to receive the smallest effective dose to avoid withdrawal symptoms, even if this means requiring a second dose.

Costs and resource use

The panel judged the costs associated with the various routes of administration to be currently low, noting some uncertainty of the pricing of specifically designed products for lay administration currently under development.

Feasibility

While judging naloxone administration in a variety of dosages to be feasible in all settings, the panel noted IV administration would be less appropriate for laypersons, where preference for IM or IN modes may be more appropriate.

Intranasal use of naloxone is currently an improvised, "off-label" method of administration which has not passed through regulatory procedures.

RECOMMENDATION 2 (KEY QUESTIONS 2 AND 3)

Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting and local context.

Strength of recommendation: Conditional **Quality of evidence: Very low**

REMARKS

Route of administration

- The GDG recognizes that the IV route is appropriate and effective in medical settings.
- Parenteral use of naloxone (IV, IM, SC) requires sterile injection equipment.
- The capacity of the nasal mucosa to absorb liquids is limited, so if the intranasal route of administration is to be used, concentrated forms of naloxone should ideally be used.
- The GDG has made this recommendation fully aware that the intranasal route is currently an off-label (non-licensed) route.
- Affordability may dictate the preferred route in particular contexts.

Dosage

- The choice of initial dose will depend on the formulation of naloxone to be used and the context.
  - In medical settings dose selection is not generally an issue as dose titration is standard practice. In non-medical settings dose titration is not so easily accomplished and higher initial doses may be desirable.
  - The context also dictates the total amount of naloxone made available to non-medical responders. More than one dose may need to be available in a non-medical setting. The initial dose should be 0.4 mg–2 mg, targeting recovery of breathing. In most cases 0.4–0.8 mg is an effective dose. It is important to provide sufficient naloxone to supplement the initial dose, as necessary.
  - Intranasal delivery may require a higher dose. It should be noted that the commonly used method of intranasal administration is to spray 1 ml of the 1 mg/ ml formulation of naloxone into each nostril with an atomizer connected to a syringe.
- Where possible, efforts should be made to tailor the dose to avoid marked opioid withdrawal symptoms. The GDG notes that higher initial doses above 0.8 mg IM/IV/SC are more likely to precipitate significant withdrawal symptoms.
- A more complicated situation arises where there has been an overdose of a combination of drugs. In this situation naloxone is still beneficial for reversing the opioid intoxication component of the overdose.
- It is essential that expert professional assistance be sought as soon as possible. Even in the case of opioid overdose, a person may not respond to naloxone if other drugs have been taken.

Decision on strength of recommendation: The GDG decided to make this a conditional recommendation because, while there was certainty that the benefits outweighed the harms and that the end-users favoured this recommendation, there was uncertainty about the costs of intranasal naloxone, as this is currently an "off-label" use.

Key question 4 – cardiopulmonary resuscitation (see Annex 4 for details)

Background

Until recently, the standard approach to cardiopulmonary resuscitation (CPR), regardless of aetiology, has been to clear the airway, provide rescue breathing and perform chest compression (the "ABC" approach – airway, breathing, circulation). However, in the past decade there has been concern that bystanders are not willing or able to provide rescue breathing effectively and that this may delay the use of chest compression. As a result, some international guidelines now recommend that layperson bystanders responding to cardiac arrest use chest compression only cardiopulmonary resuscitation (COCPR) *(63, 65)*.

The cardiac arrest seen in opioid overdose occurs as a result of progressive respiratory failure and metabolic disturbances. Because the aetiology in this type of cardiopulmonary arrest is primarily respiratory in origin, provision of traditional resuscitation, using rescue breathing as well as chest compressions, may be needed.

Key question

Should the resuscitation response to suspected opioid overdose, including by layperson bystanders, be based on standard CPR or chest compression only CPR?

Systematic review

Of the 5594 studies screened, none fulfilled the eligibility criteria set initially, but there were a number of trials comparing CPR to COCPR for out-of-hospital cardiac arrest of unspecified origin.

Evidence to recommendations

Summary of findings

Since there have been no studies comparing CPR to COCPR in the management of opioid overdose, the quality of direct evidence in favour of one approach over the other is very low.

Benefits and harms

A number of trials provide indirect evidence related to the benefits and harms of CPR and COCPR in opioid overdose. A study in Melbourne of bystander-administered CPR for heroin overdose found the provision of CPR, compared with no CPR, was associated with a lower rate of hospitalization (13.9% vs. 17.7% P<0.05) *(70)*. A meta-analysis of CPR versus COCPR for non-specific arrest found COCPR to be associated with increased survival compared with standard CPR (RR 1.22 [1.01–1.46]) *(71)*, however this did not identify the sub-population of interest – people with opioid-induced cardiac arrest.

Chest injuries from CPR are common, but age dependent. The incidence of rib fractures varied from 12.9% to 96.6% while for sternal fractures it was 1.3% to 43.3%, but these do not appear to affect survival *(76)*. The incidence of fractured ribs is lower in younger populations *(76)*.

The panel judged the benefits of any CPR to outweigh the risks, including due to its misapplication. The panel judged early naloxone provision to be a fundamental component of the CPR response in suspected opioid overdose. While noting the trend for the use of COCPR in non-opioid-induced cardiac arrest, the panel concluded that, in suspected opioid overdose, there is a clear benefit from effectively administered rescue breathing in combination with chest compressions and a potential harm from not providing rescue breathing. Given the clear and strong benefits of naloxone, the panel also advised that the resuscitation approach used should be one that does not delay the initial administration of naloxone.

Values and preferences

The observational studies reviewed in Annex 2, report that lay first responders are willing to, and do, administer CPR, including rescue breathing. Respondents to the online values-and-preferences survey indicated a high level of preparedness to give both chest compressions and rescue breathing to people experiencing opioid overdose.

There was a preference for use of barrier devices when providing rescue breathing. People at risk of overdose indicated they wished to receive chest compressions and rescue breathing if naloxone was not available.

Costs and resources

It was noted that while training is required for bystanders to correctly implement CPR, performance of all forms of CPR consumes few resources.

Feasibility

All forms of CPR were shown to be feasible in all studies, notwithstanding potential cultural issues with rescue breathing, including mouth-to-mouth resuscitation.

RECOMMENDATION 3 (KEY QUESTION 4)

In suspected opioid overdose, first responders should focus on airway management, assisting ventilation and administering naloxone.

Strength of recommendation: Strong **Quality of evidence[1]: Very low**

REMARKS

Because the key feature of opioid overdose is respiratory arrest, ventilation is a priority. While recognizing there are different protocols in different parts of the world, the GDG suggests the following steps in resuscitating an individual with suspected opioid overdose.

- Apply vigorous stimulation[2], check and clear airway, and check respiration – look for chest rising and falling.
- In the presence of vomit, seizures or irregular breathing, turn the patient on their side, and, if necessary, clear the airway of vomit.
- In the absence of regular breathing provide rescue ventilation and administer naloxone.
- If there are no signs of life, commence chest compressions.
- Re-administer naloxone after two to three minutes if necessary.
- In all cases call for professional assistance.
- Monitor the person until professional help arrives.
- Where available, CPR mouth barriers should be used for rescue ventilation.

Decision on strength of recommendation: The GDG determined that the recommendation should be strong despite the very low quality of the evidence because of the life-saving nature of CPR, including rescue breathing, in suspected opioid overdose in the community, and the low likelihood of resuscitation-induced harm. The panel also noted the feasibility of, and strong preferences in favour of CPR, including rescue breathing, expressed both by those at risk of overdose and those likely to witness an opioid overdose.

[1] The quality of evidence refers to the clinical trial evidence on the key question (comparing different approaches to resuscitation in opioid overdose) rather than the clinical trial evidence for resuscitation *per se*.

[2] The most common way of applying vigorous physical stimulation to someone who is not responding to verbal stimulation is to rub the person's sternum (breast bone) with one's knuckles.

Key question 5 – post-resuscitation care (see Annex 5 for details)

Background

For the purpose of these guidelines, post-resuscitation care refers to the period immediately following the successful reversal of opioid overdose with naloxone. Successful reversal is indicated by the full restoration of consciousness, or effectively "walking and talking normally".

The half-life of naloxone is substantially shorter than the half-life of some opioids, resulting in a risk of rebound toxicity when the naloxone "wears off". Consequently, post-resuscitation care in long-acting overdoses may need to be prolonged.

Key question

What should be the response to opioid overdose after the administration of naloxone and successful reversal of opioid overdose in the community, including by lay first responders?

Systematic review

Of the 5594 studies screened, none fulfilled eligibility criteria regarding the subsequent management of overdose with short-acting opioids following reversal with naloxone.

One RCT assessed the management of methadone (a long-acting opioid) overdose in opioid-naïve individuals using naltrexone, a specific sub-population at risk of overdose from long-acting opioids. As it was agreed

during the meeting to limit the scope of the guidelines to opioid overdose care in the community, the use of naltrexone, which is not considered appropriate for lay administration, was excluded from further consideration in these guidelines.

Five observational studies relevant to the question were identified. These studies, which investigated appropriate criteria for discharge from care or observation, were confined to post-hoc examinations of ambulance or emergency department datasets, cross-referencing specific medical examiner databases and were all from high-income countries (see Annex 5).

Evidence to recommendations

Summary of findings

Five observational studies assessed mortality risk following opioid overdose reversal with naloxone by ambulance staff and discharge on-scene. One prospective study which linked pre-hospital emergency care and forensic examiners' databases over 10 years, identified 3245 individuals treated for opioid overdose, 2241 of whom were released on-scene. Rebound opioid toxicity was identified in three of 14 deaths recorded within 48 hours of receiving naloxone (0.13% – 3/2241 from rebound opioid toxicity, 0.62% all-cause mortality) *(77)*. A further three retrospective studies linking emergency medical services (EMS) and forensic examiners' datasets reported no deaths within 12 hours of naloxone reversal in 1661 pre-hospital opioid overdoses where the individuals were either discharged on-scene or refused further observation *(78–80)*. A retrospective review of hospital emergency department admissions following transportation after being treated for opioid overdose reported that 97% of 444 transported individuals were discharged from care without further intervention *(81)*.

Benefits and harms

The panel decided that there is a potential for harm from rebound opioid toxicity following reversal of opioid overdose with naloxone in the community if the person who has overdosed is left unsupervised. This risk of harm can be reduced considerably if the first responder remains with the person who has overdosed until after the effects of naloxone have "worn off" and monitors their breathing and level of consciousness.

A normal level of consciousness (Glascow Coma Scale [GCS] score 15), "walking and talking" normally and normal breathing pattern (respiratory rate > 10) indicate recovery.

The panel did not make a recommendation on subsequent management of long-acting opioid overdose as such overdoses should be managed in hospitals and the scope of these guidelines was limited to the management of opioid overdose in the community setting.

Values and preferences

The majority of street-based drug users report staying with people who have overdosed *(69)*. Family members and friends of people at risk of overdose also indicated they would stay with the person who has overdosed. People who come across people who have overdosed in the course of their work would expect to do the same.

Costs and resources

The panel judged that there are minimal financial consequences of remaining with a person recovering from opioid overdose for several hours. On the other hand, routine transfer to hospital requires considerable use of resources.

Feasibility

While noting that all studies concerning the post-naloxone management of short-acting opioid overdose have been conducted in high-income countries, the panel agreed that discharge on-scene following opioid overdose recovery is feasible in most settings. The panel was not able to assess the feasibility of layperson observation and "discharge" following recovery as no data was available to evaluate this component of care.

RECOMMENDATION 4 (KEY QUESTION 5)

After successful resuscitation following the administration of naloxone, the affected person should have their level of consciousness and breathing closely observed until they have fully recovered.

Strength of recommendation: Strong **Quality of evidence: Very low**

REMARKS

- This recommendation is made with knowledge of the extended duration of opioid overdose, especially with the variety of longer-acting opioids and opioid formulations in current usage. It is critical to appreciate that the witness cannot tell what the length of action will be without observing the person who has overdosed. It is important to increase awareness of the need to remain with the person who has overdosed.
- Ideally, observation should be performed by properly-trained professionals. This applies particularly where the overdose is due to the use of long-acting opioids. The period of observation needed to ensure full recovery is at least two hours, following overdose from short-acting opioids such as heroin. It may be longer where a longer acting opioid has been consumed.
- If a person relapses into opioid overdose, further naloxone administration may be required.
- The definition of 'fully recovered' is a return to pre-overdose levels of consciousness two hours after the last dose of naloxone.
- After the overdose has been reversed, the person who has overdosed should be reminded not to use opioids and other drugs that will interfere with their recovery from the overdose.
- It is important to ensure that the person who is resuscitated understands what happened and the risks of what might happen next. It should also be recognized that this is "a teachable moment" – an opportunity to offer discussion of a range of treatment options and to train the person in the prevention and management of any future overdoses.

Decision on strength of recommendation: The GDG determined that this should be a strong recommendation despite the low quality of evidence due to the ethical barriers to testing this with randomized control trials. The GDG is aware that the short half-life of naloxone, coupled with difficulty ascertaining the dose and type of opioid taken, means that naloxone may cease to be effective before the person has fully recovered but the simple nature of the proposed intervention is unlikely to result in any harm, and the willingness of people likely to witness an overdose to remain with people who have overdosed is documented.

RESEARCH PRIORITIES AND GAPS

Epidemiology/strategic information

There is a need for better epidemiological data as recent estimates of overdose incidence are restricted to high-income countries. Monitoring systems of fatal and non-fatal overdoses, as well as routine toxicology analysis of possible overdose deaths will facilitate this.

There is uncertainty about the magnitude of the benefit from a wider availability and lay use of naloxone and resuscitation, including the impact on mortality and health-care utilization. Such data, if combined with data on the cost of implementing these recommendations, would be useful for cost-effectiveness and cost-benefit analyses. Suggested study designs include monitoring the proportion of witnessed overdoses that are fatal and the proportion of fatal overdoses that are witnessed following the increased availability and use of naloxone as well as controlled prospective studies between sites that have increased availability of naloxone and those that have not.

Route of administration and dose of naloxone in the pre-hospital setting

Questions remain about the optimal dosing and formulation for the intranasal route of administration. This could be addressed by a pharmacokinetic study and tested in a RCT.

The preference of people who have overdosed for lower initial doses could be tested in a RCT, comparing time to response, need for subsequent dose and adverse effects.

It is not clear how much naloxone should be carried by lay first responders to cover all likely overdoses. This could be addressed by monitoring the doses used in the field.

Resuscitation in the pre-hospital setting by lay first responders

It is unclear if resuscitation is needed in combination with naloxone or only if there is no response to naloxone. The role of rescue breathing for lay responders in opioid overdose is inadequately understood given that hypoventilation and subsequent hypoxia is the causative mechanism.

Post-resuscitation care in the pre-hospital setting

Relative and absolute indications for transfer to hospital following opioid reversal remain unclear, in particular in the context of suspected long-acting opioid use.

In addition, key management steps in the treatment of complex overdoses (such as those due to buprenorphine and benzodiazepines) remain poorly understood, including the role of benzodiazepine reversal agents.

Naltrexone has been investigated in the management of accidental long acting opioid overdose in the opioid naiive. While naltrexone was not considered appropriate for lay administration in these guidelines, it may have a role in hospital settings. There has been limited investigation of the opioid antagonist nalmefene, which may have a role as a longer acting alternative to naloxone.

PLANS FOR DISSEMINATING, ADAPTING AND IMPLEMENTING THESE RECOMMENDATIONS

These recommendations will be used to provide guidance on the identification and management of opioid overdose in the community setting through a number of derivative publications, including model training materials and an implementation manual. These will be widely disseminated via the WHO regional and country offices, collaborating centres, professional organizations and partner agencies.

These recommendations will be adapted for the field by developing suitable training materials in consultation with regional, national and local stakeholders. Adaptation will include translation into appropriate languages and ensuring that the interventions are acceptable in local sociocultural contexts and suitable for local health systems.

Evaluating the impact of these recommendations

The impact of these recommendations will be measured in the following ways:

- the number of countries that implement programmes to increase the availability of naloxone and provide training in the management of opioid overdose to people likely to witness an opioid overdose;
- the number of countries in which naloxone is available for out-of-hospital care by paramedics;
- the WHO survey of resources for the prevention and treatment of substance use disorders;
- the number of countries that produce guidelines on the use of naloxone in the management of opioid overdose in the pre-hospital setting consistent with these WHO guidelines;
- an assessment of the number of references to the WHO guidelines in the medical literature;
- measurement of opioid overdose deaths and the proportion of witnessed opioid overdoses that are fatal, both where naloxone has been provided and where naloxone has not been provided.

Review date

It is not expected that these recommendations will need to be reviewed until 2017. However, developments in the field will be continually monitored and should there be significant changes in practice and/or the evidence base that affect any of the recommendations, review may be undertaken earlier.

ANNEX 1
SYSTEMATIC REVIEW SEARCH STRATEGY

Methods

Inclusion criteria

Study type

Systematic reviews
Randomized control trials
Controlled prospective studies
Published in a peer-reviewed journal, or presented as an abstract at a scientific conference, between 1 January 1966 and 1 January 2014

Populations

People who use opioids (oral or parenteral)

Types of interventions

Defined by PICO question

Types of comparison

Defined by PICO question

Outcome measures

Selected by GDG for each question and ranked by importance

Search methods

Electronic searches

The following electronic databases were searched:

- Medline (1966 to present)
- EMBASE (1980 to present)
- Cochrane library
- WHO library (2000 to present)
- Clinicaltrials.gov
- International Clinical Trials Registry Platform
- Psychinfo (1980 to present)
- Cinahl (1982 to present)
- Toxline (1965 to present)

Search terms

Search Strategy (Pubmed)		
#	**Searches**	**Results**
1	"Drug Overdose"[Mesh] OR overdose* OR OD [TIAB] OR "over dose" [TIAB] OR "over dosage" [TIAB] OR "over dosed" [TIAB] OR "over dosing" [TIAB]	23090
2	"toxicity" [Subheading] OR "Toxicity Tests"[Mesh] OR toxicity [TIAB] OR poisoning [TIAB] OR "Poisoning"[Mesh] OR "poisoning" [Subheading]	695864
3	"Heroin"[Mesh] OR "Heroin Dependence"[Mesh] OR Opiate*[TIAB] OR Opioid*[TIAB] OR Diamorphine [TIAB] OR Diacetylmorphine [TIAB] OR Diagesil [TIAB] OR Diamorf [TIAB] OR Morphine [TIAB] OR Diacetylmorphine Hydrochloride [TIAB] OR Heroin [TIAB] OR "Opioid-Related Disorders" [MH] OR "Opium"[Mesh] OR Opium [TIAB] OR hydrocodone [TIAB] OR Buprenorphine [TIAB] OR codeine [TIAB] OR dextroproxyphene [TIAB] OR fentanyl [TIAB] OR hydromorphone [TIAB] OR meperidine [TIAB] OR morphine [TIAB] OR morphine [MH] OR oxycodone [TIAB] OR pentazocine [TIAB] OR sufentanil [TIAB] OR tramadol [TIAB] OR hydrocodone [MH] OR buprenorphine [MH] OR codeine [MH] OR extroproxyphene [MH] OR fentanyl [MH] OR hydromorphone [MH] OR meperidine [MH] OR opium [MH] OR oxycodone [MH] OR pentazocine [MH] OR sufentanil [MH] OR tramadol [MH]	141562
4	(#1 OR #2) AND #3	25487
5	Naloxone [MH] OR naloxone [TIAB] OR antioplaz [TIAB] OR en 1530 [TIAB] OR en 15304 [TIAB] OR en1530 [TIAB] OR en15304 [TIAB] OR l n allyl 14 hydroxynordihydromorphinone [TIAB] OR maloxone [TIAB] OR mapin [TIAB] OR n allyl 7 8 dihydro 4 hydroxynormorphinone [TIAB] OR n allylnoroxymorphone hydrochloride [TIAB] OR naloxone [TIAB] OR nalone [TIAB] OR nalonee [TIAB] OR narcan[TIAB] OR narcan neonatal [TIAB] OR narcanti [TIAB] OR narcon [TIAB] OR narvcam [TIAB] OR naxone [TIAB] OR zynox [TIAB] OR Nalone [TIAB] OR Naloxonratiopharm [TIAB] OR MRZ-2593[TIAB] OR MRZ 2593[TIAB] OR MRZ2593[TIAB]	28476
6	"Flumazenil"[Mesh] OR Flumazepil [All fields] OR Romazicon [All fields] OR Lanexat [All fields] OR Anexate [All fields] OR "Ro 15 1788" [TIAB] OR "Ro 151788" [TIAB] OR mazicon [TIAB] OR "ym 684" [TIAB] OR ym684 [TIAB]	4338
7	"Cardiopulmonary Resuscitation"[Mesh] CPR [TIAB] OR Code Blue [TIAB] OR Mouth-to-Mouth [TIAB] OR Basic Cardiac Life Support [TIAB] OR "assisted ventilation" [TIAB] OR " bag valve mask ventilation" [TIAB] OR "pocket mask " [TIAB] OR resuscitation [TIAB] OR "Heart Massage"[Mesh] OR heart massages [TIAB] OR Heart massage [TIAB] OR cardiac massage [TIAB] OR cardiac massages [TIAB]	42178
2	#5 OR #6 OR #7	72661
9	#4 AND #8	23604
10	"animals" [Mh] NOT ("animals"[MH] AND "humans" [MH])	3854040
11	#9 NOT #10	7084
12	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR randomly [tiab] OR trial [tiab] OR groups [tiab] OR Random* [TIAB] OR "cohort studies" [MH] OR cohort* [TW] OR "controlled clinical trial" [PT] OR "epidemiologic methods" [MH] OR "case-control studies" [MH] OR (case [TW] AND control*[TW]) OR (case [TW] AND series [TW])	5554641
13	#11 AND #12	2730

Data collation and extraction

Selection of studies

The initial screening was carried out by a single reviewer who inspected the search hits by reading titles and abstracts. Following this, each potentially relevant study located in the search was obtained in full text and assessed for inclusion independently by two reviewers. In doubtful or controversial cases, all identified discrepancies were discussed in order to reach consensus on all items.

Citations identified through computer database searching were initially screened into the following categories:

Yes – for articles clearly meeting the inclusion criteria for the review.

Pull to check – for articles which may meet the inclusion criteria; the full text of the article must be reviewed before final decision about inclusion can be made.

No – for articles clearly not meeting the inclusion criteria for the review; no further consideration is necessary.

Other evidence referred to in the guidelines

Additional scientific literature is referred to in the guidelines to provide background and contextual information, and to assist in the completion of the balance between benefits and harms, values and preferences, and feasibility sections of the "evidence to recommendations" profiles. This evidence was not searched for systematically.

A separate online survey and key informant interviews were also conducted to inform the values and preferences section (see Annex 6).

ANNEX 2
KEY QUESTION 1 – EVIDENCE PROFILE AND DECISION TABLE

Key question 1

Should naloxone be distributed to people who are likely to witness an opioid overdose?

PICO formulation of key question for evidence synthesis

Population: People likely to witness an opioid overdose

Intervention: Provision of naloxone, and training in its administration in the management of opioid overdose

Comparison: Treatment as usual (no provision of naloxone outside medical settings)

Outcomes: (see below)

OUTCOMES SELECTED AND RANKED BY THE GDG FOR KEY QUESTION 1

Outcome	Importance
Overdose mortality	Critical
Overdose complication (such as aspiration)	Critical
Overdose morbidity (prolonged adverse outcome of opioid overdose)	Critical
Time to administer naloxone	Critical
Time to opioid overdose reversal	Critical
Opioid withdrawal reaction to naloxone	Important
BBV transmission through unsafe injection	Important
Unsafe injection related injury	Important
Adverse effect of resuscitation	Important
Psychosocial intervention / referral to treatment post overdose	Important

Evidence

Of the 5594 studies screened, no studies fulfilled the eligibility criteria:

- systematic reviews – none
- randomized controlled trials – none
- controlled prospective studies – none.

Other evidence

Although no studies met the eligibility criteria, observational evidence identified in the systematic search that met all PICO criteria other than the comparison group/study design were examined for information on the outcomes under consideration (see Tables 4, 5 and 6, below).

TABLE 4. CHARACTERISTICS OF CASE SERIES EXAMINING THE PROVISION OF TAKE-HOME NALOXONE

Study	City, country	Population (n=), number followed up (if known)	Intervention training; equipment received	OD witnessed, naloxone present, naloxone used; resuscitation performed	Outcomes	Comments
Bennet 2012	Wales, UK (5 public sites + 3 prison locations)	N=525 (521 opiate users + 4 non-users), of which n=362 from community sites and n=163 from prison locations. 28 followed up when requesting more naloxone. 6 months follow up	Taught facts and myths about opiate OD, how to identify signs of OD and respond, trained in use of naloxone, given practice for IM injection, CPR training and first aid; 1x 0.4 mg naloxone vials and needles for IM administration	26 ODs witnessed, 0 experienced, 26 naloxone present, 26 naloxone used; 21 (81%) used recovery position, 10 (40%) used CPR, 23 (85%) called an ambulance	1 death (4%); no other adverse effects reported	
Dettmer 2001	Jersey, UK	101 opiate misusers in contact with local drug services	Instructed on IM injection and wider principles of resuscitation from OD and recovery; 2x 0.4 mg prefilled naloxone syringes	Naloxone used 5 times; CPR not reported	No deaths or adverse events reported other than withdrawal symptoms	
Dettmer 2001	Berlin, Germany	124 opiate misusers attending a healthcare project – 40 followed up	Trained in emergency resuscitation and OD management; 2 naloxone ampoules (0.4 mg each), needles and syringes	Naloxone used 29 times by 22 people; CPR not reported	No deaths; 10 instances (34%) where naloxone provoked a sudden onset of opiate withdrawal	In 31% of cases EMS were involved
Doe-Simkins 2009	Boston, USA	N=385 potential bystanders, 278 followed up	Participants instructed to deliver 1 ml (containing 1 mg) to each nostril of the overdose victim and trained in overdose management; 2 lure-lock pre-filled syringes with 2 mg/2 ml naloxone hydrochloride and the mucosal atomization device	74 reported reversals by 50 different people; CPR not reported	No deaths; in 2 cases naloxone precipitated withdrawal symptoms but in both cases the victim did not use additional opiates to alleviate the symptoms. In 2 cases naloxone wore off, one after 20 minutes but ambulance took over care and in other naloxone was re-administered after 90 minutes.	EMS were involved in 21 of the 74 reported overdoses (28%). During four overdoses bystanders could not connect the mucosal atomization device to the syringe, but each resulted in successful reversals. Four people who used naloxone supply were not initially enrolled in the programme.
Enteen 2010	San Francisco, USA	Opioid users (N=1942)	Taught mechanisms and risk factors of opioid OD, prevention strategies, recognition, response, calling EMS, administration of naloxone (IM), rescue breathing, aftercare, naloxone care, logistics and refills; 2 x 0.4 mg naloxone vials, 2 syringes and 1 rescue breathing mask.	399 reported responses where naloxone was administered; 123 performed sternum rub, 127 awoke OD victim, 199 performed rescue breathing	6 deaths (2%) and 36 outcomes unknown (9%); 3 cases of seizure (1%), 50 cases of vomiting (13%), 36 victims angry/'dope sick' (9%)	5% reported using multiple prescriptions during multiple OD events. Participants called 911 only during minority (29%) of naloxone administrations.

Study	City, country	Population (n=), number followed up (if known)	Intervention training; equipment received	OD witnessed, naloxone present, naloxone used; resuscitation performed	Outcomes	Comments
Galea 2006	New York City, USA	N=25 opioid users, 22 participants were successfully followed up in the first 3 months after initial enrolment	Taught to assess OD, call EMS, recovery position, rescue breathing and naloxone administration; 2 x 0.4 mg vials of naloxone, needles and syringes	11 (50%) participants reported witnessing a total of 26 overdoses during the follow-up period. Among the 17 most recent OD witnessed, naloxone was administered 10 times; 4 cases of mouth to mouth or cardiopulmonary resuscitation	No deaths reported where naloxone was used, of those without naloxone, 5 lived, 1 died and the outcome of 1 was unknown; no adverse effects reported	
Kan (in press)	Kyrgyzstan, Tajikistan	N=217 people who inject drugs (158 Kyrgyzstan + 59 Tajikistan)	Taught OD prevention, use of naloxone; not specified.	Of 1046 ampoules received 589 were administered; CPR not reported	Not reported	
Leece (2013)	Toronto, Canada	N= 209 people using opioids	Taught OD prevention and assessment of symptoms, call EMS, chest compressions, naloxone administration, post OD case, naloxone storage and management of naloxone induced withdrawal symptoms; 2 x 0.4 mg ampoules of naloxone, needles and syringes	17 administrations of naloxone and all survived; CPR not reported	No deaths reported; no adverse effects reported	The programme had a high recruitment rate (average 26 users per month).
Lopez Gaston (2009)	Birmingham and London, UK	N=70 patients with opioid dependence, 6 month follow up	Taught to recognize OD and response, discussed causes of opiate OD, and naloxone administration; 1x 0.4 mg prefilled naloxone syringe	16 witnessed, naloxone used by ambulance on 3 occasions; 2 cases of mouth-to-mouth resuscitation	No deaths where naloxone was used; no adverse effects were reported and 2 of the 3 were taken to hospital	Knowledge reported at the end of the training appeared to predict whether people would retain the naloxone (if clear about its use they were more likely to retain the medication). Also it was found that people keep their naloxone at home and don't have access to them at the overdose situation. They don't want to carry because of stigma (conflict with recovery) and police issues

Study	City, country	Population (n=), number followed up (if known)	Intervention training; equipment received	OD witnessed, naloxone present, naloxone used; resuscitation performed	Outcomes	Comments
Maxwell 2008	Chicago, USA	N= 1120, 340 PWID In contact with outreach workers and additional 780 people in contact with the PWID	Taught basic opioid neurophysiology, pharmacodynamics and pharmacokinetics of commonly used opiates, pharmacology and pharmacokinetics of naloxone and other opiate antagonists, risk factors and prevention techniques for opiate OD, signs and symptoms for the early recognition of opiate OD, prevention of choking and aspiration in the unconscious patient, techniques of rescue breathing, routes of administration and dosing guidelines for naloxone, and protocols for follow-up care; 10 ml multi-dose vial of naloxone, 0.4 mg/ ml, a supply of syringes and needles, a pocket size instruction card and documentation that the medication is legal and medically sanctioned	319 reported peer overdose reversals. 5 cases did not respond until 2nd injection given (however 4 of these cases were given within less than two minutes of the first and may not have been clinically needed); CPR not reported	1 death where other drugs were also detected, 1 case of vomiting, 1 case of seizures (history of alprazolam use reported); 1 report of using 5 sequential doses, each having a partial revival effect before full reversal was achieved	Approximately 1/3 of the reversals occurred in persons who were reinstituting heroin use after a period of abstinence. In many cases, this period was as brief as 3 days (hospital detox programme or incarceration). The experience of reversing an overdose has been reported to be a powerful bonding experience with the users and a significant other
Mcauley 2009	Lanarkshire, Scotland, UK	19 PWID, follow up at 2 and 6 months	Given similar training curriculum to Strang 2009 and practice of IM injection; 1 x 0.4 mg naloxone prefilled syringe, sharps bin, needles, swabs and gloves	3 witnessed with 2 successful naloxone revivals; CPR pilot -training procedure followed on both occasions	1 death; no adverse effects or inappropriate use reported	A buddy was required to come along to the training session. This was a problem for recruitment at some points. Refresher trainings and replacement of naloxone were offered. There was one false claim of naloxone usage detected.
Piper 2008	New York, USA	N=122	Taught overdose prevention education and naloxone administration. Also discussed rescue breathing practice, method of cooperating with police and medical staff post-naloxone administration and the importance of talking to drug users' partners about naloxone and OD response; 2 x prefilled naloxone syringes (1 mg/ ml), prescription as proof of legitimacy of the medication, rescue breathing mask, written information summarizing OD revival steps	71 reported witnessing overdoses, 50 of those 71 used naloxone. 68 reported successful revivals; CPR not reported	14 (17.1%) outcomes were unknown; no adverse effects were mentioned	Participants reported calling an ambulance in 74% of the times where naloxone was used

Study	City, country	Population (n=), number followed up (if known)	Intervention training; equipment received	OD witnessed, naloxone present, naloxone used; resuscitation performed	Outcomes	Comments
Seal 2005	San Francisco, USA	n=24 street opioid injectors, followed up at 6 months	Taught to identify a heroin OD, risk factors and prevention strategies for an OD, use of naloxone and practiced CPR, calling EMS, administration of naloxone; 2 x 0.4 mg naloxone prefilled syringes (individually prescribed), gloves, rescue breathing mask and detailed instructions, safe compartment for used needles	20 heroin OD witnessed, naloxone administered in 15; CPR administered in 16	No deaths; no adverse effects reported	New argument raised regarding cost-effectiveness comparing with CPR interventions. Ambulance involved in 10% of the overdoses recorded.
Strang 2009	England, UK	n=239 opioid using patients of drug treatment services, FU n=186, followed up at 3 months	Taught risks factors and how to recognize an OD, response to an OD and naloxone administration; 91% of the sample received a naloxone supply	16 OD witnessed, naloxone administered in 11; CPR not reported	1 death where naloxone was not present; 4 reports of withdrawal symptoms and dissatisfaction from the individual injected with naloxone	28% have subsequently trained another person.
Tobin 2009	Baltimore, USA	n=250 street drug users, FU=85, followed up at 6 months	Taught risk factors, sign and symptoms of opiate OD and strategies for preventing opiate OD and trained in IM injection, rescue breathing and recovery position; 3 x 5 ml syringes with intramuscular needles, one 10 ml reusable vial of 0.4 mg/ ml naloxone, face shield, sharp containers, prescription for naloxone refills	48 OD witnessed, naloxone used in 22; CPR not reported	Not reported	Slight decrease of ambulance calls from 65% to 49%
Wagner 2009	Los Angeles, USA	n=96 homeless PWID, FU = 47, followed up at 3 months	Taught skills (call EMS, rescue breathing, administration of naloxone) to prevent, recognize, and respond to opiate OD; 2 x 0.4 mg/1 ml naloxone prefilled syringe, latex gloves, alcohol swabs, a rescue breathing mask, a small card describing the response techniques	35 OD witnessed, 28 ODs received naloxone; 25% applied vigorous stimulation, 60% called ambulance	4 (11.4%) deaths and 5 (14.3%) unknown outcomes (was not specified if naloxone was given to those who died); 4% of victims got angry and 3% vomited	No change observed in attitudes, increase in knowledge observed
Wheeler 2012	USA - 48 distribution programs in 15 states + DC	n=53032, FU not specified, mostly less than 12 months	Training varied; equipment given also varied	10,171 OD in which naloxone used; CPR practices varied	Not reported	43.7% of programmes reported problems obtaining naloxone (cost & supply issues)
Yokell 2011	Rhode Island, USA	n=120, FU n=10 at 3 months	Taught common causes of OD, techniques for prevention, proper and improper responses, and administration of IM naloxone; 10ml flip top multi-dose vial of naloxone, syringes, needles, printed materials with instructions on OD response	10 witnessed overdoses, 5 administered naloxone; 5 participants used techniques learned in OD response training without administering naloxone	Not reported	

TABLE 5. CHARACTERISTICS OF INTERRUPTED TIME SERIES ANALYSIS STUDY

Study	City, country	Population (n=), number followed up (if known)	Intervention	Overdoses witnessed	Outcomes	Comments
Walley 2013	Massachusetts, USA	N=2912 received naloxone and training in 19 communities with 5 or more fatal opioid overdoses per year	Persons likely to witness an overdose were given 2 prefilled syringes of naloxone (2 mg/2 ml), two mucosal atomization devices, training in OD management including rescue breathing, administering intranasal naloxone, and staying with OD victim until EMS arrives/ person recovers	327 ODs witnessed and rescue attempted, naloxone used in 153, 38% (123/327) performed rescue breathing, 89% (287/321) stayed with victim awake or help arrived; 33% contacted EMS	No deaths out of 153 overdoses in which naloxone was used; other adverse events not reported	In three cases the naloxone did not revive the OD victim but in each case the person survived with medical care

TABLE 6. OUTCOMES OF NALOXONE DISTRIBUTION IN CASE SERIES STUDIES

Study	N = (provided naloxone and training)	Dose and formulation dispensed	Followed up	Overdoses witnessed	Resuscitations attempted	Naloxone used	Died[1]	Mortality rate[4]	Opioid withdrawal reaction to naloxone	Other adverse events
Bennett 2012	525	1 x 0.4 mg IM	28	—	—	28	1/28	3.5%	—	—
Dettmer 2001	101	2 x 0.4 mg IM	NA	NA	NA	5	0/5	0%	Withdrawal symptoms	0
Dettmer 2001	124	2 x 0.4 mg IM	40	NA	NA	29	0/29	0%	10 withdrawal	0
Doe-Simkins 2009	385	2 x 2 mg IN	278	—	—	74	0/74	0%	2 withdrawal	0
Enteen 2010	1942	2 x 0.4 mg IM	399	—	—	399	6/399	1.5%	36 angry 50 vomiting	3 seizures
Galea 2006	25	2 x 0.4 mg IM	22	26	—	10/17[2]	0/17	0%	0	0
Kan 2014a	158	—	—	131	—	246	—	—	—	—
Kan 2014b	59	—	—	83	—	103	—	—	—	—
Leece 2013	209	2 x 0.4 mg IM	—	—	—	17	0/17	0%	0	0
Lopez Gaston 2009	70	1 x 0.4 mg IM	46	16	—	—	0/16	0%	0	0
Maxwell 2008	1120	1 x 4 mg IM[3]	319	—	—	319/?	1/319	0.31%	1 vomiting and withdrawal	1 seizures
Mcauley 2009	19	1 x 0.4 mg IM	17	3	3	2	1/3	33.3%	—	—
Piper 2008	122	2 x 1 mg IM	71	71	71	82	0/68 (14 unknown)	0%	—	—
Seal 2005	24	2 x 0.4 mg IM	24	20	19	15	0/20	0%	—	—
Strang 2009	239	—	186	16	—	10	1/16	6.25%	4 withdrawal	0
Tobin 2009	250	1 x 4 mg IM[3]	85	48	—	22	—	—	—	—
Wagner 2009	93	2 x 0.4 mg IM	47	35	—	28	4/30 (5 unknown)	13.3%	—	—
Walley 2013	2912	2 x 2 mg IN	—	—	—	327	0/327	0%	—	—
Walley 2013b	1553	2 x 2 mg IN	—	—	—	92	—	—	—	—

Study	N = (provided naloxone and training)	Dose and formulation dispensed	Followed up	Overdoses witnessed	Resuscitations attempted	Naloxone used	Died[1]	Mortality rate[4]	Opioid withdrawal reaction to naloxone	Other adverse events
Wheeler 2012	53 032	—	—	—	—	10171	—	—	—	—
Yokell 2011	120	1 x 4 mg IM[3]	10	10	—	5	0/10	0%	0	0

[1] The denominator is sometimes the number witnessed and sometimes the number of overdoses treated with naloxone.
[2] 17 most recent overdoses witnessed.
[3] 4 mg multi-dose vials – used in either 0.4 mg or 0.8 mg aliquots.
[4] The mortality rate is the crude proportion of deaths per witnessed overdose in the follow-up period of the study (generally 3-6 months), not an annual mortality rate.

SUMMARY OF FINDINGS TABLE – KEY QUESTION 1

Outcomes of overdoses witnessed by persons given naloxone and training in its use

Patient or population: Injecting drug users, peers, and family members

Settings: Community

Intervention: Naloxone distribution

Outcomes	Importance (critical, important)	Illustrative comparative risks* (95% CI)		Studies	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
		Control	Overdose witnessed by person given naloxone and training				
Overdose mortality**	Critical	No control group	1.0% (0.83% to 1.21%)	15 studies[1]	1368	⊕◯◯◯ VERY LOW	
Overdose complication (such as aspiration)	Critical	—	—	—	—		No such complications were reported although they were not specifically excluded
Overdose morbidity (prolonged adverse outcome of opioid overdose)	Critical	—	—	—	—		No such outcomes were reported although they were not specifically excluded
Time to administer naloxone	Critical	—	—	—	—		Not reported
Time to opioid overdose reversal	Critical	—	—	—	—		Not reported
Opioid withdrawal reaction to naloxone	Important	No control group	7.6% (4.9% to 10.2%)	8 studies[2]	887	⊕◯◯◯ VERY LOW	
Psychosocial intervention/ referral to treatment post overdose	Important	—	—	—	—		Not reported
Unsafe injection related injury	Important	—	—	—	—		No unsafe injections were reported although it was not specifically reported as an outcome
Adverse effect of resuscitation (seizures)	Important	No control group	0.45% (0.43% to 0.47%)	9 studies[3]	892	⊕◯◯◯ VERY LOW	

Outcomes	Importance (critical, important)	Illustrative comparative risks* (95% CI)		Studies	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
		Control	Overdose witnessed by person given naloxone and training				
BBV transmission through unsafe injection	Important	—	—	—	—	⊕◯◯◯ VERY LOW	No unsafe injections were reported although it was not specifically reported as an outcome

GRADE working group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

* As uncontrolled case series, none of the studies produce an estimate of the effect size of the intervention and are not graded. They are, by default, the lowest grade of evidence.

**The overdose mortality is the crude proportion of deaths per witnessed overdose in the follow-up period of the study (generally 3-6 months), not an annual mortality rate.

[1] Bennett (2012); Dettmer (2001); Dettmer (2001); Doe-Simkins (2009); Enteen (2010); Galea (2006); Leece (2013); Lopez Gaston (2009); Maxwell (2008); Mcauley (2009); Piper (2008); Seal (2005); Strang (2009); Wagner (2009); Walley (2013a).
[2] Dettmer (2001 - Berlin); Doe-Simkins (2009); Enteen (2010); Galea (2006); Leece (2013); Lopez Gaston (2009); Maxwell (2008); Strang (2009).
[3] Dettmer (2001; Dettmer (2001); Doe-Simkins (2009); Enteen (2010); Galea (2006); Leece (2013); Lopez Gaston (2009); Maxwell (2008); Strang (2009).

Evidence to recommendation framework

Summary of evidence

There were no studies that met the inclusion criteria for the review.

Balance of benefits versus risks and harms

Benefits versus risks and harms

Although there were no studies that met the inclusion criteria of the systematic review, there were 20 studies reporting some data on the provision of naloxone to people likely to witness an opioid overdose ("take-home" naloxone). They describe more than 50 000 doses of naloxone distributed in the USA alone. Of those that were followed up, the average mortality rate in witnessed overdoses was 1.0% (0.83% to 1.21%). Although there was no comparator in these studies, the mortality rate following overdoses has previously been estimated at 2–4% *(9)*. An analysis of uncontrolled studies reveals that mortality rates are low in those administered naloxone (1.0% [0.83% to 1.21%]). The interrupted-time-series analysis found that take-home naloxone was associated with lower overdose death rates (aRR 0.73 [0.57 – 0.91]).

Acute withdrawal syndrome from administration of naloxone is possible, although it is short lived (approximately 15 minutes). Based on the observational studies reviewed, it is likely to occur in 7.6% (4.9% to 10.2%) of resuscitation attempts with naloxone in the community. The only other adverse outcome described in the observational studies reviewed are seizures, occurring in 0.45% of cases (0.43% to 0.47%).

Values and preferences

Drug users' peers are willing to intervene in overdose events *(93)*, including administering naloxone *(40)*. Observational studies performed in the USA report that following training, approximately 55% of trained participants witnessed an overdose *(51, 55)*.

Naloxone was used in approximately 70% (ranging from 60% to 80%) of the overdoses witnessed by naloxone-trained laypersons *(50–54)*.

Often people who witness an opioid overdose do not know which actions to take during witnessed overdoses *(39, 94, 95)*.

An evaluation in New York of a peer naloxone programme reported that 97 of 118 participants (82.2%) said they felt comfortable to very comfortable using naloxone if indicated, while 94 of 109 (86.2%) said they would want a bystander to administer naloxone to them if they were overdosing *(55)*.

There are case reports of self-administration of naloxone, including reports of self-administration of intranasal naloxone *(96)*.

A survey in 2003 of prescribers (physicians, physician's assistants, nurse practitioners; n = 363) examining their willingness to prescribe naloxone for individuals at risk of overdose found 33.4% willing, 29.4% unsure and 37.1% unwilling *(97)*. A 2007 survey in USA found that 54% of physicians were unwilling to prescribe naloxone, though 23% had not heard of naloxone, suggesting that physician education might be necessary to improve knowledge and potential willingness *(98)*.

Resource use

Wastage of naloxone appears low. One pilot study in central Asia found high usage rates (51%–83%) and low wastage rates (3.1%). A modelling study projected that wastage rates over four years would be between 3%–14% *(99)*.

Trained peers manage their take home naloxone carefully. In Scotland, a follow-up of 17 peers six months after having been given naloxone training reported all 17 still had their take home naloxone. Key-workers validated this in 15 individuals *(100)*. There was no evidence of inappropriate use in the three cases where naloxone was administered.

In 2008, as part of the PONI (Preventing Overdose and Naloxone Intervention) project in Rhode Island, an estimate for the cost of treating overdose events in Rhode Island's emergency departments (327 visits) was USD $88 288, with an additional minimum of $827 637 spent on hospital admissions related to overdose events. This yielded a total of $915 925 in overdose-related hospital costs for 2008, which the authors calculated could have been used to purchase over 61 000 kits of naloxone *(102)*.

A peer distribution programme for naloxone in Toronto estimated if one life was saved out of 17 individuals administered naloxone for overdose, the programme would cost CAD $30 890–$46 335 per quality adjusted life year (QALY) gained *(103)*.

A recent study found the distribution of naloxone to heroin users for lay-person administration to be cost-effective in both the American and Russian context *(104, 105)*. In the US scenario, naloxone distribution cost USD $438 per QALY gained (CI, $48 to $1706), and if heroin use was considered a net cost to society the cost per QALY gained increased to USD $2429 (CI, $1305 to $3986)(105). In the Russian context the cost per QALY gained was USD $94, but this cost would be higher if other societal costs of heroin use were included *(106)*. Both cost-effectiveness analyses were based on modelled data.

The cost of naloxone varies enormously as it is a low-volume product and there is often only one distributor in a country. There are reports the cost of naloxone has gone up tenfold in recent years in the US. The website 'naloxone.info' lists where naloxone may be purchased and prices for a 0.4 mg/ ml vial range from USD $0.38 in China to USD $0.51 in France to USD $50 in Sweden. One product which claims to be the only one specifically marketed for lay administration sells for US $27 for a pack containing one 2 ml prefilled syringe of 1 mg/ ml naloxone and two needles in a tamper proof case.

Feasibility

Naloxone distribution appears feasible in most socioeconomic settings however there are a number of implementation issues, including the selection of participants, the training in overdose management and resuscitation, and legal issues in the distribution of a prescription medicine and the use of a prescription medicine by laypersons.

Identification of individuals for take home naloxone

Project Lazarus, in North Carolina, developed a set of criteria to screen individuals for eligibility for take home naloxone prescriptions. Thirteen indicators were identified. These included:

- recent medical treatment for overdose
- suspected non-medical use of opioids
- high dose prescription (> 100 mg morphine equivalence/day)
- methadone prescriptions for opioid naïve individuals
- recent release from jail or drug treatment
- those in OST programmes
- any opioid prescription in those with a significant medical co-morbidity
- remoteness
- voluntary request *(49)*.

Training

A number of studies documented significant increases in identification of overdose and correct indication for the administration of naloxone.

An RCT from the UK found knowledge and attitudes relating to overdose and naloxone administration improved to a greater extent in the intervention arm (structured training) compared to basic information only three months after completion of the intervention *(60)*.

Published papers suggest the length and style of training necessary for naloxone distribution and administration is variable. Training can be delivered in a teaching session *(54)*, friendly dialogue, group discussion or on a drop-in basis *(53)*. The session can take as little as 10 minutes *(55–57)* or as long as eight hours *(58)*. Even very short trainings in naloxone indications can increase the accuracy in overdose identification.

In the Boston Public Health Commission naloxone distribution programme, while training for health professionals and employed staff was eight hours, bystander training was 15 minutes *(56)*.

A study of 70 individuals with opioid dependence in two sites in the UK found knowledge retention six months after training in the identification and treatment of overdose to be well preserved *(101)*.

Legal

Naloxone is a prescription-only medication in most countries, but it is available over the counter in Italy. In the UK and the US (at the state level) special regulations for naloxone administration in an emergency situation and 'good Samaritan' laws are available to protect the physician and clients from legal action *(107, 108)*. In the UK, naloxone is on a list of medications that can be legally administered by anyone in an emergency *(109)*.

DECISION TABLE: RECOMMENDATION 1

The GDG considered the following when making their decision on the strength of the recommendation:

Factor	GDG response
Is there high or moderate-quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	No
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes
Are the expected values and preferences clearly in favour of the recommendation?	Yes
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes

Strength of recommendation: the GDG decided to set the strength of the recommendation as **'Strong'**.

ANNEX 3
KEY QUESTIONS 2 AND 3 – EVIDENCE PROFILES AND DECISION TABLE

The close relationship between route of administration and dosage resulted in these two PICO questions overlapping substantially, so they were therefore considered together in the one review.

Key question 2

What formulation of naloxone should be used in the management of opioid overdose, including by lay responders, in the pre-hospital setting?

PICO formulation of key question for evidence synthesis

Population: People with opioid overdose in the community setting
Intervention: Use of intranasal route of administration of naloxone
Control: Use of intramuscular or subcutaenous route of administration of naloxone
Outcomes: (see below)

OUTCOMES SELECTED AND RANKED BY GDG FOR KEY QUESTION 2

Outcome	Importance
Overdose mortality	Critical
Overdose complication (such as aspiration)	Critical
Overdose morbidity (prolonged adverse outcome of opioid overdose)	Critical
Opioid withdrawal reaction to naloxone	Critical
Time to administer naloxone	Critical
Time to opioid overdose reversal	Critical
Ease of administration	Critical
BBV transmission through unsafe injection	Important
Unsafe injection related injury	Important
Adverse effect of resuscitation	Important
Psychosocial intervention / referral to treatment post overdose	Important

Key question 3

What dose of naloxone should be used initially in the management of opioid overdose?

PICO formulation of key question for evidence synthesis

Population: People with opioid overdose in the community

Intervention: Single dose approach (use of 0.8 mg IM or higher as an initial dose, or equivalent dose of alternative IV or IN formulation)

Comparison: Titrated dose approach (use of 0.2-0.4 mg IM as an initial dose with view to repeating the dose as needed, or equivalent dose of IV or IN formulation)

Outcomes: (see below)

OUTCOMES SELECTED AND RANKED BY GDG FOR KEY QUESTION 3

Outcome	Importance
Overdose mortality	Critical
Overdose complic ation (such as aspiration)	Critical
Overdose morbidity (prolonged adverse outcome of opioid overdose)	Critical
Opioid withdrawal reaction to naloxone	Critical
Time to opioid overdose reversal	Critical
Time to administer naloxone	Important
Psychosocial intervention / referral to treatment post overdose	Important
BBV transmission through unsafe injection	Not important
Unsafe injection related injury	Not important

Background

Naloxone hydrochloride is available in 0.02 mg, 0.4 mg and 1 mg per 1 ml vials, a 4 mg/10 ml multi-use vial, and 2 mg/1 ml, 2 mg/2 ml and 2 mg/5 ml prefilled syringes for intravenous (IV), intramuscular (IM) and subcutaneous (SC) injection. It is currently not under patent and available as a generic product.

The recommended dosage and route of administration provided by manufacturers' product literature on management of opioid overdose is 0.4 to 2 mg via IM, IV or SC injection, repeated as necessary, up to a total dose of 10 mg.

Current international recommendations on the dose and route of naloxone used for reversal of opioid overdose vary. The European Resuscitation Council Guidelines do not specify a route and recommend that *initial doses of naloxone be 400 µg IV, 800 µg IM, 800 µg SC* or *2 mg IN (65)*. The 2010 International Consensus on Cardiopulmonary Resuscitation Guidelines do not specify a dose but recommend *naloxone be given intravenously or intramuscularly. Intranasal or tracheal routes may be used if conditions preclude IV* or *intramuscular administration (63)*. The American Heart Association Guidelines recommend dose titration (from 0.04 mg or 0.4 mg upwards) and state naloxone can be given IV, IM, intranasally, and into the trachea *(64)*.

The above guidelines recommend that airway maintenance and assisted ventilation commence prior to the administration of naloxone for individuals in respiratory depression but not in cardiac arrest.

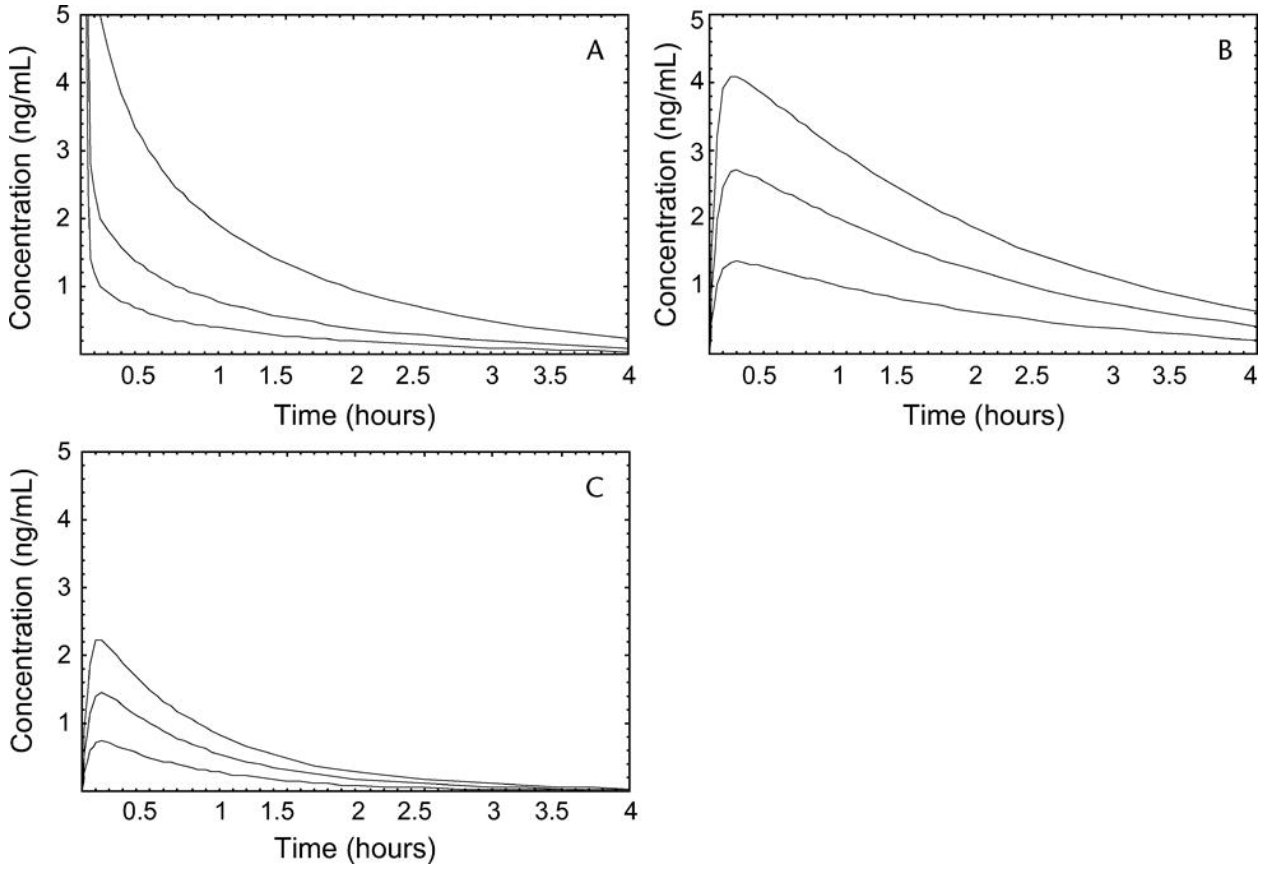
The IV route requires intravenous access. Intramuscular and SC routes do not require IV access, but require a needle. The IN route does not require a needle – typically the syringe is attached to a mucosal atomization device.

The main adverse event associated with naloxone use for reversal of opioid intoxication is an acute opioid withdrawal syndrome, characterised by agitation and anxiety, nausea, myalgia and sweating *(110)*. Avoidance (or reduction) of these symptoms is the rationale using a lower initial dosage (e.g.0.04 mg) titrated until effect is achieved with multiple boluses of increasing dosage *(9, 111)*. The European Resuscitation Council guidelines recommend titration of the naloxone dose.

Naloxone pharmacokinetics and pharmacodynamics

A pharmacokinetic analysis of naloxone in six healthy male volunteers (median Ht 1.78, Wt 80 kg, age 25) monitored drug levels following: 1) 0.8 mg intravenous (IV) naloxone; 2) 0.8 mg intramuscular (IM) naloxone; 3) 0.8 mg intranasal (IN) naloxone; 4) 2 mg intravenous naloxone; and 5) 2 mg intranasal naloxone. Naloxone 400 µg/1 ml was used. Following these results, a covariate model was developed in which 1000 potential patients were simulated for each of the four arms of the study (0.8 mg and 2 mg IV, 0.8 mg IM, and 2 mg IN). The median time to peak naloxone concentration ranged from 12 minutes for intramuscular administration to between six and nine minutes for intranasal administration. The bioavailability for naloxone administered IN was 4% of that for IV and for IM bioavailability was 35% of that for IV. The simulated nomograms are illustrated below.

FIGURE 1. SIMULATED NALOXONE NOMOGRAMS FOR A) IV NALOXONE 0.4, 0.8, AND 2 MG; B) INTRAMUSCULAR DOSES 0.8, 1.6 AND 2.4 MG; AND C) INTRANASAL DOSES 2, 4, AND 6 MG (C).*(112)*



The authors state that the large volume of IN naloxone (up to 6 ml in each nostril in the 6 mg protocol) administered led to some being swallowed and subject to first pass metabolism, hence reducing the effective total dose *(112)*.

A laboratory experiment examining IV administered naloxone's ability to antagonise morpine (IV) in human subjects reported that naloxone exhibited clinical effect in 1–2 minutes and peak effect in 30 minutes. The duration of action of 0.2 mg of naloxone was between 1 and 1.5 hours; that of 0.4 mg was between 1.5 and 2 hours, while 0.8 mg of naloxone resulted in an effect persisting beyond 4 hours *(113)*.

Results of the literature search

Of the 5594 studies screened, two RCTs fulfilled eligibility criteria for key question 2 *(66, 67)*. Both were field-based RCTs conducted in Victoria, Australia where paramedics administered either IN or IM naloxone in the pre-hospital setting to suspected opioid overdose patients. No studies met the criteria for key question 3.

Characteristics of included studies

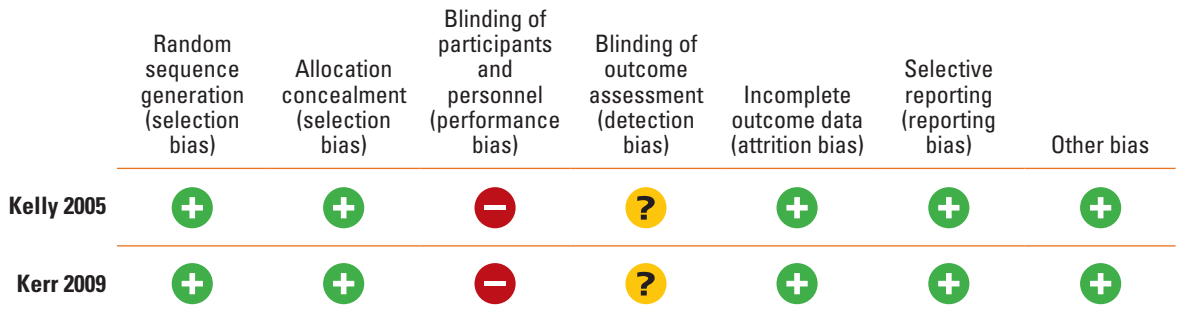
Kelly 2005	
Methods	LOCATION Rural and metropolitan Melbourne, Victoria, Australia SETTING Metropolitan Ambulance Service (MAS) and Rural Ambulance Victoria (RAV). These services provide almost 100% of emergency ambulance response in Victoria. DURATION OF RECRUITMENT 5 January 2002 – 19 December 2003 DURATION OF TRIAL ~24 months OBJECTIVE To compare IN naloxone (2 mg/2 ml) to IM naloxone for suspected OD. **Randomized controlled trial** Patients received either 2 mg IN naloxone (1 mg into each nostril) or 2 mg IM naloxone and supportive care for suspected opioid overdoses in the pre-hospital setting IN was via mucosal atomization device (1 mg (1 ml) via each nostril) Failure to respond at 8 minutes given rescue dose of 0.8 mg IM naloxone Post OD care was recovery/discharge at scene or transport to hospital
Participants	INCLUSION CRITERIA Suspected opioid OD and unrousable EXCLUSION CRITERIA Nil stated STUDY POPULATION 182 enrolled and randomized (IN 98, IM 84) 27 excluded IN – 7 regained consciousness prior to treatment, 4 incomplete data, 3 technical problems IM – 5 regained consciousness prior to treatment, 5 incomplete data 155 in final sample included for analysis (Intranasal 84, intramuscular 71)
Interventions	INTERVENTION Intranasal naloxone 2 mg via mucosal atomization device (1 mg / 1 ml via each nostril) CONTROL Intramuscular naloxone 2 mg RESCUE NALOXONE (inadequate response at 8 minutes) Intramuscular naloxone 0.8 mg

Kelly 2005	
Outcomes	PRIMARY Response time, defined as the time to regain a respiratory rate greater than 10 per minute SECONDARY Proportion of patients with a respiratory rate greater than 10 per minute at 8 minutes Proportion of patients with GCS score greater than 11 at 8 minutes Proportion requiring rescue naloxone **Rate of adverse events** The proportion of the IN group for whom IN naloxone alone was sufficient treatment was also examined
Notes	ETHICS Royal Melbourne Hospital Human Research Ethics Committee INFORMED CONSENT Requirement for individual patient consent was waived (inclusion criteria was patient was unrousable) Subjects were informed of their enrolment in the study by way of a study information brochure when they regained consciousness FUNDING William Buckland Foundation

Kerr 2009	
Methods	LOCATION Melbourne, Australia SETTING Six branches of Metropolitan Ambulance Service, which capture ~50% of all heroin OD in Melbourne DURATION OF RECRUITMENT 1 August 2006 – 13 January 2008 DURATION OF TRIAL 16 months OBJECTIVE To compared concentrated IN naloxone (2 mg/ ml) to IM naloxone for suspected OD Random allocation (opened envelope at scene) for paramedics (trained) to administer 2 mg IN or 2 mg IM naloxone and supportive care for suspected opioid overdoses in the pre-hospital setting IN was via mucosal atomization device (1 mg/0.5 ml via each nostril) Failure to respond at 10 minutes given rescue dose of 0.8 mg IM naloxone. Post OD care was recovery/discharge at scene or transport to hospital
Participants	INCLUSION CRITERIA Suspected opioid OD (altered LOC, myosis, RR<10)+ unrouseable (GCS ≤ 12) EXCLUSION CRITERIA No major facial trauma, blocked nasal passages or epistaxis. STUDY POPULATION 266 patients treated 178 randomized 6 excluded (3 become alert prior, 3 missing equipment) so 83 intranasal (IN) 89 intramuscular (IM) 172 included in the analysis (83 IN, 89 IM)
Interventions	INTERVENTION Intranasal naloxone 2 mg via mucosal atomization device (1 mg–0.5 ml via each nostril) CONTROL Intramuscular naloxone 2 mg RESCUE NALOXONE (inadequate response at 10 minutes) Intramuscular naloxone 2 mg

Kerr 2009	
Outcomes	PRIMARY Proportion of patients with an adequate response within 10 minutes of naloxone administration defined as spontaneous respirations at a rate ≥ 10 per minute and/or GCS ≥ 13 (those having 2 doses of naloxone marked as inadequate, no matter the time frame) SECONDARY Time to adequate response Hospitalization **Adverse event rate** Drug-related vomiting, nausea, seizure, sweating, tremor, acute pulmonary oedema, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, cardiac arrest, agitation and paraesthesia Administration related nasal obstruction, nasal deformity Study-related epistaxis, ruptured septum, spitting, coughing, leakage of solution from nasal passages Requirement for 'rescue' naloxone due to inadequate primary response as judged by the treating paramedics.
Notes	ETHICS Melbourne Health Human Research Ethics Committee INFORMED CONSENT Requirement for individual patient consent was waived (inclusion criteria was patient was unrousable) Subjects were informed of their participation by way of an information letter after regaining consciousness which allowed them to withdraw themselves from the study or seek further information FUNDING Drug Policy and Services, Department of Human Services, Melbourne, Victoria, Australia

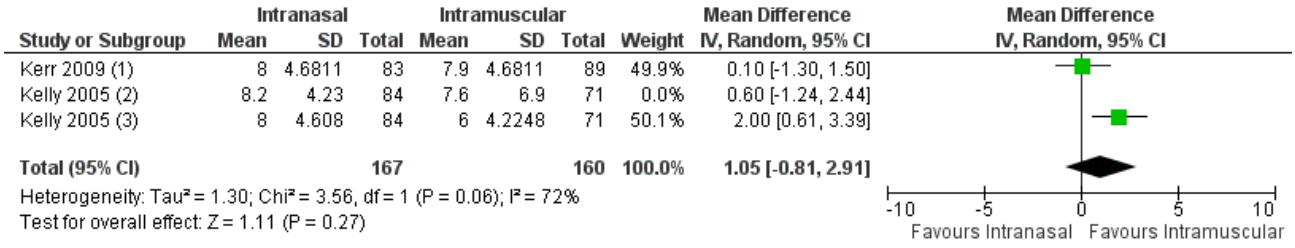
Risk of bias



Forest plots by outcome

FIGURE 1 (ANALYSIS 1.1)

Forest plot of comparison 1: intranasal versus intramuscular naloxone; outcome 1.1: time to opioid overdose reversal



(1) RR ≥ 10 and/ or GCS ≥13
(2) GCS > 11
(3) RR ≥ 10/min

FIGURE 2 (ANALYSIS 1.2)

Forest plot of comparison 1: intranasal versus intramuscular naloxone; outcome 1.2: rescue naloxone given

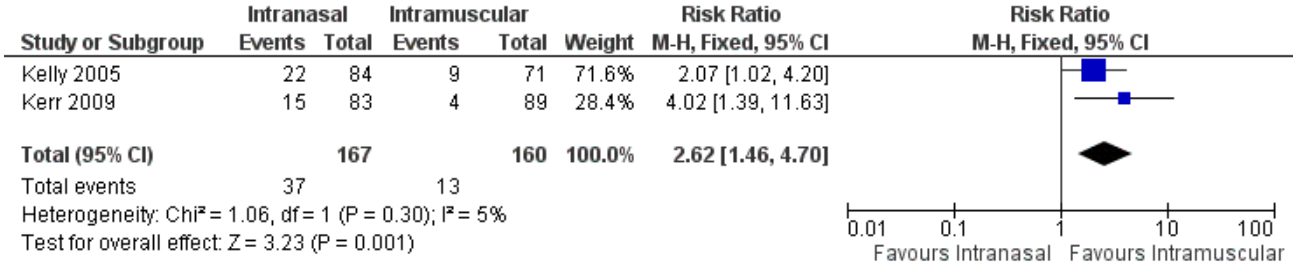


FIGURE 3 (ANALYSIS 1.3)

Forest plot of comparison 1: intranasal versus intramuscular naloxone; outcome 1.3: adverse events (minor)

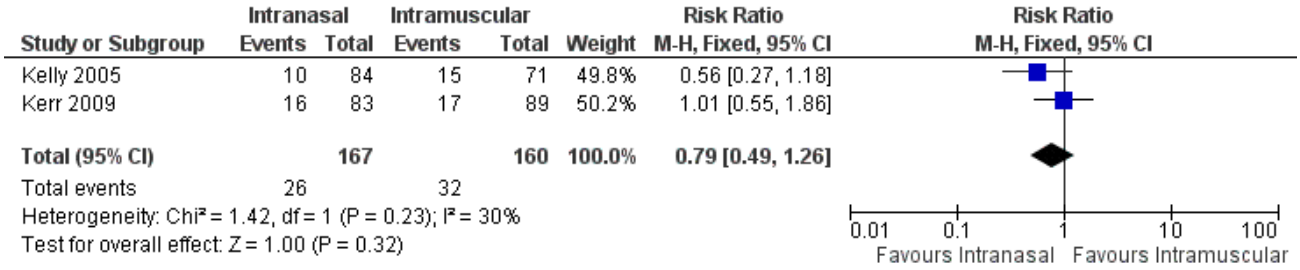
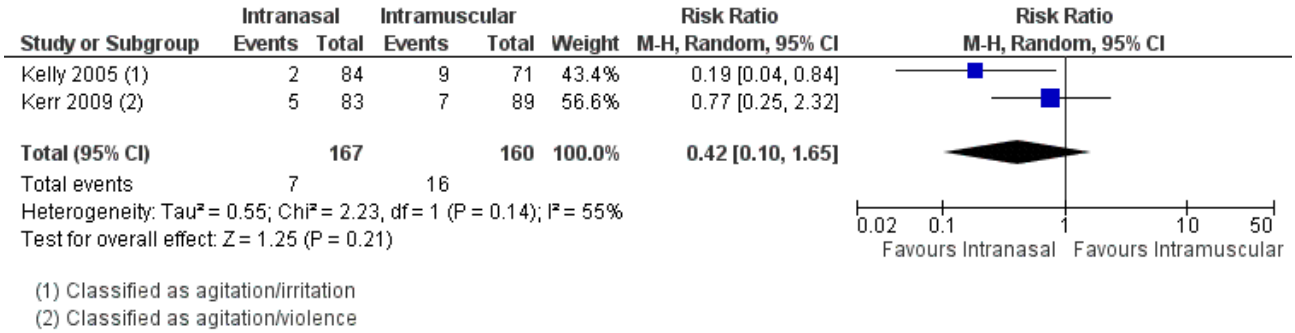


FIGURE 4 (ANALYSIS 1.4)

Forest plot of comparison 1: intranasal versus intramuscular naloxone; outcome 1.4: opioid withdrawal reaction to naloxone (agitation/irritation/violence)



(1) Classified as agitation/irritation
(2) Classified as agitation/violence

FIGURE 5 (ANALYSIS 1.5)

Forest plot of comparison 1: intranasal versus intramuscular naloxone; outcome 1.5: adverse events (major)

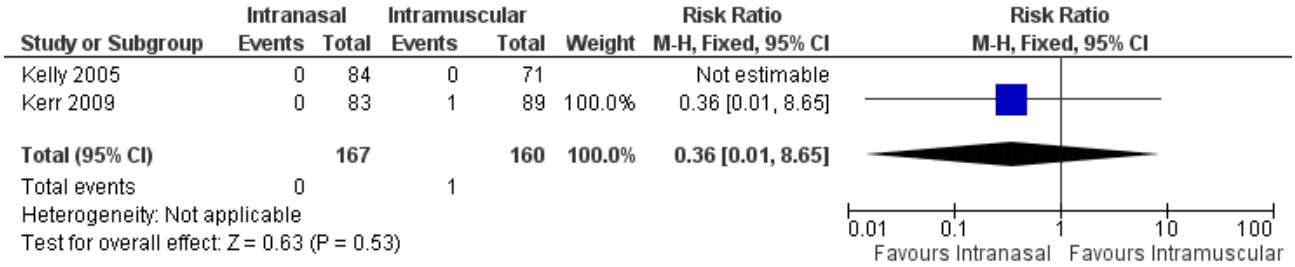
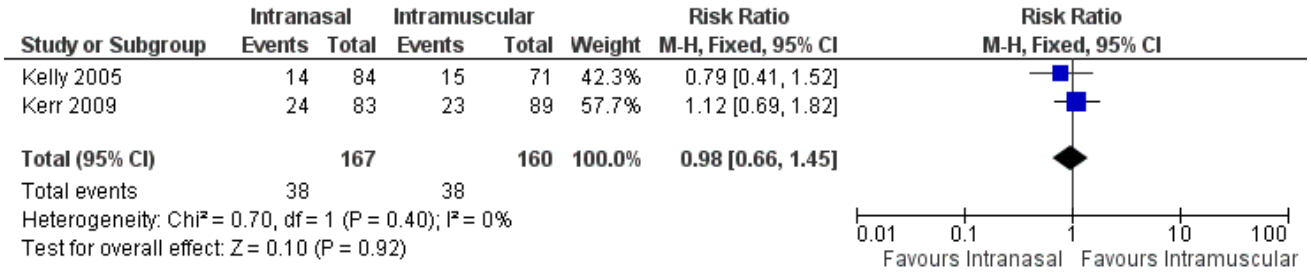


FIGURE 6 (ANALYSIS 1.6)

Forest plot of comparison 1: intranasal versus intramuscular naloxone; outcome 1.7: hospitalisation



SUMMARY OF FINDINGS TABLE – KEY QUESTION 2

Intranasal compared to intramuscular administration of naloxone for opioid overdose

Patient or population: patients with opioid overdose

Settings: pre-hospital setting

Intervention: intranasal

Comparison: intramuscular

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intramuscular	Intranasal				
Mortality	See comment	See comment	Not estimable	—	See comment	Not reported
Ease of administration[1]	See comment	See comment	Not estimable	—	See comment	Not reported
Time to administration	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Overdose complication Adverse event (major)	**6 per 1000**	**2 per 1000** (0 to 54)	**RR 0.36** (0.01 to 8.65)	327 (2 studies)	⊕◯◯◯[2,3,4,5] VERY LOW	
Overdose morbidity	**794 per 1000**	**675 per 1000** (564 to 818)	**RR 0.85** (0.71 to 1.03)	327 (2 studies)	⊕⊕◯◯[2,6,7] LOW	
Opioid withdrawal reaction to naloxone Agitation/irritation/ violence	**100 per 1000**	**42 per 1000** (10 to 165)	**RR 0.42** (0.1 to 1.65)	327 (2 studies)	⊕◯◯◯[2,8,9] VERY LOW	
Time to opioid overdose reversal Mean response time (mins)			The mean time to opioid overdose reversal in the intervention groups was **1.05 higher** (0.81 lower to 2.91 higher)[10]	327 (2 studies)	⊕⊕◯◯[2,6,11] LOW	
Blood borne virus transmission						Not reported
Referral to treatment post overdose						Not reported

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intramuscular	Intranasal				
Rescue naloxone given	**81 per 1000**	**213 per 1000** (119 to 382)	**RR 2.62** (1.46 to 4.7)	327 (2 studies)	⊕⊕◯◯[2,12,13] LOW	

* The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval. **RR:** Risk ratio.

GRADE working group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Neither of the trials reported this specifically. In Kelly 2005, 3 technical problems with Intramuscular were noted, not clearly associated with ease of administration.
[2] Risk of bias: rated as serious. Although the studies were conducted well, lack of blinding may have resulted in performance bias and possible detection bias.
[3] Inconsistency: result comes from a single study (seizure in IM arm of Kerr 2009)
[4] Indirectness: not downgraded. The two trials measured major adverse events which may or may not be related to overdose or naloxone administration.
[5] Imprecision: rated as very serious. Only one event with a very wide confidence interval.
[6] Inconsistency: not downgraded (note I^2 = 49%). This may be driven by the difference in time measurement of adequate response (Kelly – 8 vs. Kerr – 10 mins) and the magnitude of outcome parameters (Kelly – GCS > 11, RR > 10, Kerr – GCS ≥ 13, RR ≥ 10)
[7] Indirectness: marked as serious. Adequate response (as measured by RR or GCS at 8–10 minutes) is a proxy measure for overdose morbidity
[8] Inconsistency: rated as serious. Measured as agitation/irritability in Kelly; measured as agitation/violence in Kerr. Unlikely to explain heterogeneity
[9] Imprecision: rated as serious. Low event rate, wide confidence intervals.
[10] Complete aggregated (Kelly) or disaggregated (Kerr) data not available. Included data in Kerr (GCS/RR), Kelly (RR only).
[11] Imprecision: rated as serious. The confidence interval crosses the line of no effect and appreciable harm.
[12] Inconsistency: not downgraded. While in Kelly 2005 rescue naloxone was given at 8 minutes and in Kerr 2009 at 10 minutes, this was no sufficient to justify downgrading (I2 = 5%)
[13] Indirectness: rated as serious. Administration of 'rescue' naloxone is a proxy measure for time to reversal as it indicates a delayed response.

GRADE EVIDENCE TABLE – KEY QUESTION 2

Author(s): Nick Walsh, Nandi Siegfried, Nicolas Clark
Date: 2014-02-15
Question: INTRANASAL VS. INTRAMUSCULAR ADMINISTRATION OF NALOXONE FOR OPIOID OVERDOSE
Settings: pre-hospital setting
Bibliography: Walsh N, Siegfried N. and N. Clark. Intranasal naloxone for opioid overdose

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intranasal	Intramuscular	Relative (95% CI)	Absolute	Quality	Importance
Mortality – not reported												
2	—	—	—	—	—	None	—	—	—	—		CRITICAL
Ease of administration – not reported[1]												
2	—	—	—	—	—	None	—	—	—	—		CRITICAL
Time to administration												
2	No evidence available	—	—	—	—	None	—	—	—	—		CRITICAL
Adverse events (major)												
2	Randomized trials	Serious[2]	No serious inconsistency[3]	No serious indirectness[4]	Very serious[5]	None	0/167 (0%)	1/160 (0.63%)	RR 0.36 (0.01 to 8.65)	4 fewer per 1000 (from 6 fewer to 48 more)	⊕◯◯◯ VERY LOW	MPORTANT
Opioid withdrawal reaction to naloxone (assessed with: agitation/irritation/violence)												
2	Randomized trials	Serious[2]	Serious[8]	No serious indirectness	Serious[9]	None	7/167 (4.2%)	16/160 (10%)	RR 0.42 (0.1 to 1.65)	58 fewer per 1000 (from 90 fewer to 65 more)	⊕◯◯◯ VERY LOW	CRITICAL
Time to opioid overdose reversal (measured with: Mean response time (mins); better indicated by lower values)												
2	Randomized trials	Serious[2]	No serious inconsistency[6]	No serious indirectness	Serious[10]	None	167	160	—	MD 1.05 higher (0.81 lower to 2.91 higher)[11]	⊕⊕◯◯ LOW	CRITICAL

Quality assessment							No. of patients		Effect			
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intranasal	Intramuscular	Relative (95% CI)	Absolute	Quality	Importance
Psychosocial intervention / referral to treatment post overdose												
2	—	—	—	—	—	None	—	—	—	—		IMPORTANT
Blood borne virus transmission												
2	—	—	—	—	—	None	—	—	—	—		IMPORTANT
Unsafe injection related injury												
2	—	—	—	—	—	None	—	—	—	—		IMPORTANT
Adverse events (minor)												
2	Randomized trials					None	26/167 (15.6%)	32/160 (20%)	RR 0.79 (0.49 to 1.26)	42 fewer per 1000 (from 102 fewer to 52 more)	⊕⊕◯◯ LOW	IMPORTANT

[1] Neither of the trials reported this specifically. In Kelly 2005, 3 technical problems with intramuscular administration were noted, not clearly associated with ease of administration
[2] Risk of bias: rated as serious. Although the studies were conducted well, lack of blinding may have resulted in performance bias and possible detection bias.
[3] Inconsistency: result comes from a single study (seizure in IM arm of Kerr 2009).
[4] Indirectness: not downgraded. The two trials measured major adverse events which may or may not be related to overdose or naloxone administration.
[5] Imprecision: rated as very serious. Only one event with a very wide confidence interval.
[6] Inconsistency: not downgraded. Note $I^2 = 49\%$. This may be driven by the difference in time measurement of adequate response (Kelly – 8 vs. Kerr – 10 mins) and the magnitude of outcome parameters (Kelly – GCS > 11, RR > 10, Kerr GCS ≥ 13, RR ≥ 10).
[7] Indirectness: marked as serious. Adequate response (as measured by RR or GCS at 8–10 minutes) is a proxy measure for overdose morbidity.
[8] Inconsistency: rated as serious. Measured as agitation/irritability in Kelly; Measured as agitation/violence in Kerr. Unlikely to explain heterogeneity.
[9] Imprecision: rated as serious. Low event rate. Wide confidence intervals.
[10] Imprecision: rated as serious. The confidence interval crosses the line of no effect and appreciable harm.
[11] Complete aggregated (Kelly) or disaggregated (Kerr) data not available. Included data in Kerr (GCS/RR), Kelly (RR only).
[12] Inconsistency: not downgraded. While in Kelly 2005 rescue naloxone was given at 8 minutes and in Kerr 2009 at 10 minutes, this was no sufficient to justify downgrading (I2 = 5%).
[13] Indirectness: rated as serious. Administration of 'rescue' naloxone is a proxy measure for time to reversal as indicates a delayed response.

Evidence to recommendation framework

Summary of evidence

Meta-analysis of the two eligible RCTs found no difference between the administration of intranasal naloxone (initial dose 2 mg) vs. intramuscular naloxone (initial dose 2 mg) for opioid overdose. There was no difference in the rates of overdose complications (relative risk (RR) 0.36 [0.01 to 8.65]), overdose morbidity (RR 0.85 [0.71 to 1.03]), opioid withdrawal reaction to naloxone (RR 0.42 [0.1 to 1.65]) or time to opioid reversal (mean difference (MD) 1.05 higher [0.81 lower to 2.91 higher]). There were no deaths in either study. Ease of administration was not estimable.

There were no studies examining IV administration compared to IN or IM naloxone administration in the pre-hospital setting.

There were no studies comparing different doses or dosing regimens of naloxone (such as titration versus single dose) in the pre-hospital setting.

Benefits versus harms

Dose and concentration

An RCT conducted in 2009 in Victoria, Australia, which included 172 patients treated for suspected opiate overdose in the pre-hospital setting (median age 29, 74% male) *(67)* used 2 mg/5 ml IM and 2 mg/1 ml IN naloxone. In an earlier study conducted in 2005 in Victoria, another RCT of 155 patients suspected opiate overdose and attended by paramedics in the pre-hospital setting, the naloxone dose was the same (2 mg), but the concentration of the IN differed (2 mg/2 ml) *(66)*. In the 2009 study, comparing IN and IM routes, using the higher concentration of IN naloxone, there was no significant difference between response times (8 min vs. 7.9 min) or rate of response at 10 mins (72.3% vs. 77.5%). In the 2005 study, which used a lower concentration of IN naloxone, time to respirations (>10/min) was faster in IM (6 min[5–7]) vs. IN (8min[7–8]) and the IM group was also more likely to have spontaneous respirations within 8 minutes (82% vs. 63% (p =0.0163 OR 2.6 [1.2–5.5]). This may indicate that the use of a more concentrated IN naloxone formulation results in an improved clinical response.

Route of administration

Intramuscular absorption is relatively rapid and comparable to IV in clinical effectiveness *(81)*. In head-to-head comparisons, while IM naloxone may result in a more rapid clinical response, both are equally as effective with no additional need for naloxone in the IN group *(66, 67)*.

An RCT in Victoria, Australia included 172 patients treated for suspected opiate overdose in the pre-hospital setting (median age 29, 74% male) *(67)*. Subjects were administered 2 mg/5 ml naloxone by IM or IN (2 mg/ml, 0.5 ml/nostril). Comparing IN and IM routes, there was no significant difference between response time (8 min vs. 7.9 min) or rate of response at 10 mins (72.3% vs. 77.5%). Supplementary oxygen was more often administered in the IN group (18.1% vs. 4.5%). The odds of providing rescue naloxone for inadequate response were OR 4.8 (p<0.01) comparing IN to IM. One major adverse event (seizure) was reported. There were no differences in adverse events. Agitation or withdrawal occurred in < 10% respectively in both groups.

In a second RCT in Victoria, Australia, of 155 patients suspected opiate overdoses attended by paramedics in the pre-hospital setting (median age 28–30 years, 70%–73% male), 71 individuals were treated with IM naloxone (2 mg/5 ml) and 84 with IN naloxone (2 mg/5 ml) *(66)*. Clinical response (time to respirations > 10/min) was faster in IM (6 min [5-7]) vs. IN (8min [7-8]).The IM group was also more likely to have spontaneous respirations within 8 minutes (82% vs. 63% (p =0.0163 OR 2.6[1.2-5.5]). There was no difference in the time to GCS >11 or having a GCS < 11 at 8 minutes or the proportion requiring rescue naloxone.

In the meta-analysis combining the two studies, there were no statistically significant differences between IN and IM routes of administration.

Other evidence

In a classroom based RCT in Ireland, 18 advanced paramedic trainees were randomized to IN or IV naloxone administration for a simulated suspected opioid overdose on a mannequin. The mean time taken for the IN and IV group was 87.1 seconds and 178.2 seconds respectively. The difference in mean time taken was 91.1 seconds (95%CI 55.2–126.9 seconds, $p < 0.0001$)*(120)*.

In a study comparing 1 mg naloxone IN (per 0.4 ml) to IV and IM routes in 17 opioid dependent individuals, no significant differences between any of the groups were found regarding blood pressure and heart rate changes. The authors concluded that IN administration was comparable to IV in terms of the onset of clinical effect (withdrawal symptoms), while IM onset was delayed compared to IV *(114)*.

A study of 2 mg IN naloxone (1 mg/ ml each nostril) in 30 pre-hospital patients in Utah reported a mean time to clinical response of 3.4 minutes in those who responded. Of the naloxone responders, 11/12 (91%) responded to IN naloxone alone, with 1 requiring an IV supplemental dose *(115)*.

A retrospective review of EMS records compared IN to IV naloxone in California. There was no difference in the rate of clinical response between the IN and IV groups, although the time to clinical response was delayed in the IN versus IV group (12.9 versus 8.1 minutes, $p = 0.02$). Mean time from patient contact to clinical response was not significantly different between the IV and IN groups, suggesting that although clinical response was delayed for the IN route to IV, this was compensated by the delay in achieving IV access *(116)*.

A retrospective review of patients who were administered IN or IV naloxone by paramedics in the pre-hospital setting for suspected opioid overdose in New Jersey identified 93 pre-arrest suspected opioid overdose patients, including 55 given IV naloxone and 38 given IN naloxone. Initial IV dose was between 0.4 and 2.0 mg, and initial IN dose was 2 mg (1mg each nostril) at the discretion of the paramedics. There was no difference in the respiratory rate or GCS change between IV and IN *(117)*. The mean total dose for IN (1.95 mg) was higher than IV (1.71 mg) ($p = 0.01$), though the median dose for both groups was 2 mg. The median final RR was higher for the IV group than the IN group (18 versus 16; $p = .001$). The median final GCS score was also higher in the IV group than the IN group (15 versus 12; $p = .01$). Re-dosing was more common in the IN group (42%) than in the IV group (20%) though the decision to re-dose was at the discretion of the paramedic.

A number of observational studies on provision of IN naloxone for peer administration (following training) in the treatment of suspected opioid overdose reported rates of successful reversal close to 100% *(48, 56, 118)* with no serious problems in administration and no adverse events.

Harms

Use of a higher dose carries a greater risk of inducing an acute withdrawal syndrome. The RCT of 172 patients in Victoria, Australia, comparing IN and IM naloxone for pre-hospital administration found both well tolerated with no differences observed in agitation and/or violence (IN: 6.0%, IM: 7.9%), nausea and/or vomiting (IN: 8.4%, IM: 7.9%) or headache (IN: 4.8%, IM: 3.3%) after naloxone treatment *(67)*.

In the RCT of 155 patients in Victoria, Australia, comparing IN and IM naloxone for pre-hospital administration, there was no difference in adverse events between the two groups, although agitation/irritation was higher in the IM group (13% vs. 2%, $p = 0.03$) *(66)*.

A study in Boston evaluating an intranasal naloxone training and distribution programme of 385 enrolees reported 74 successful reversals, including four individuals not enrolled in the programme. However during four overdoses, the bystanders could not connect the mucosal-atomization device to the syringe, although each nonetheless resulted in successful reversal *(56)*.

Intranasal preparations do not require a needle and therefore eliminate the risk of needlestick injury. There were no reports of injection-related adverse events to either the person with the overdose or the lay first responder in the evaluations of lay first responder naloxone programmes.

Higher-dose approaches may result in opioid withdrawal and, rarely, opioid-withdrawal- related adverse events. Lower-dose approaches may result in an increased risk of re-overdose when naloxone levels reduce.

Values and preferences

A study on naloxone distribution and administration by peers in Australia found that 74% of interviewees preferred using the intranasal route of administration *(68)*.

In a classroom-based RCT in Ireland, 18 advanced paramedic trainees were randomized to IN or IV naloxone administration for a simulated suspected opioid overdose on a mannequin. The IN route was reported as easier and safer to use than the IV route in 89% of advanced paramedic trainees *(120)*.

Naloxone 2 mg/2 ml IN administration provoked withdrawal symptoms in only 2/74 reversals *(56)*.

Resource use

There is minimal difference in cost between intranasal and intramuscular formulations.

Feasibility

Intranasal naloxone may also be used on first patient contact while IV access is obtained for additional IV naloxone if necessary to optimise time to clinical response in the case of delayed IV access *(119)*.

IV administration is essentially limited to trained health professionals.

Both intranasal and intramuscular administration of naloxone by laypersons is feasible.

Intranasal use of naloxone is an improvised "off-label" method of administration which has not passed through regulatory procedures.

DECISION TABLE: RECOMMENDATION 2

Judgements to inform the decision on the strength of the recommendation

For each of the above recommendations, the following were considered:

Factor	GDG response
Is there high or moderate-quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	No
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes
Are the expected values and preferences clearly in favour of the recommendation?	Yes
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	No

Strength of recommendation: the GDG decided to set the strength of the recommendation as **'Conditional'**.

ANNEX 4
KEY QUESTION 4 – EVIDENCE PROFILE AND DECISION TABLE

Key question 4

Should the resuscitation response to suspected opioid overdose, including by layperson bystanders, be based on standard CPR or chest compression only CPR?

PICO formulation of key question for evidence synthesis

Population: People with opioid overdose
Intervention: Standard CPR based on the "ABC" approach (attending to airway, breathing, and circulation)
Comparison: Resuscitation based on COCPR
Outcomes: (see below)

OUTCOMES SELECTED AND RANKED BY GDG FOR KEY QUESTION 4

Outcome	Importance
Overdose mortality	Critical
Overdose complication (such as aspiration)	Critical
Overdose morbidity (prolonged adverse outcome of opioid overdose)	Critical
Opioid withdrawal reaction to naloxone	Important
Adverse effect of resuscitation	Important
Psychosocial intervention / referral to treatment post overdose	Important

Background

Death from opioid overdose occurs as a result of cardiac arrest secondary to progressive respiratory failure and metabolic disturbances. Cardiac arrest is a late complication and associated with poorer outcomes as cerebral perfusion ceases at this point.

The most recent International Consensus on Cardiopulmonary Resuscitation Guidelines, the European Resuscitation Council Guidelines and the American Heart Association Guidelines recommend the commencement of airway maintenance and assisted ventilation resuscitation efforts prior to the administration of naloxone for individuals with known or suspected opioid toxicity in respiratory depression but not in cardiac arrest *(63–65)*.

There have been two key changes to international cardiopulmonary resuscitation (CPR) guidance over the last 10 years. The first was the shift from a 15:2 to a 30:2 compression-ventilation ratio for lone rescuers making quality chest compression the main focus of the resuscitation effort. The second, in 2010, was a recommendation to shift to COCPR for layperson bystanders *(63, 65)*.

Early resuscitation (e.g. CPR) of cardiac arrest (i.e. prior to pulseless electrical activity or asystole) is associated with improved outcomes *(121)* and may explain differences in survival between in-hospital and out-of-hospital cardiac arrests *(122)*, as well as survival differences between adult and paediatric arrest *(123)*.

Given the importance of ventilation over cardiac output in most opioid overdoses, and the possibility of rib and sternal fractures with external cardiac massage, there may be a case for separate resuscitation guidelines in suspected opioid overdose compared to suspected cardiac arrest.

Evidence to recommendation framework

Summary of evidence

Of the 5594 studies screened, no studies fulfilled the eligibility criteria set.

There were no studies comparing one method of resuscitation with another in suspected opioid overdose.

A meta-analysis of RCTs and prospective cohort studies that compared standard CPR to COCPR for out-of-hospital cardiac arrest was excluded as it did not specify people with suspected opioid overdose as a sub-population.

Balance of benefits versus risks and harms

Benefits of standard CPR versus COCPR

In the context of opioid overdose, respiratory depression is the primary issue.

A study in Melbourne of bystander-administered CPR for heroin overdose found the provision of CPR was associated with a lower rate of hospitalisation (13.9% vs. 17.7% p <0.05) compared with no CPR provision *(70)*.

A study of 24 PWID provided with training in naloxone and CPR in San Francisco, found that during the six-month follow-up period, 20 overdoses were witnessed by participants who provided CPR in 80% of events *(58)*.

For individuals with respiratory depression who are pre-cardiac arrest, COCPR may result in unnecessary trauma, such as fractured ribs. A 2004 non-systematic review of skeletal injuries from CPR reported the incidence of rib fractures varied from 12.9% to 96.6% while for sternal fractures it was 1.3%–43.3% *(76)*. The incidence of fractured ribs may be lower in younger populations such as children *(76)*.

In a US study of 7652 patients with out-of-hospital cardiac arrest examining bystanders' response, where COCPR was performed on non-cardiac arrest victims (including overdose), there appears to be no negative impact on survival compared to no CPR *(126)*. In contrast, a large Japanese study (n = 43 246) on COCPR and CPR for out-of-hospital cardiac arrest, found ventilation-based CPR associated with improved neurological outcomes in non-cardiac-origin cardiac arrests compared to COCPR. There was no difference in survival *(75)*.

Harms (i.e. arguments for a COCPR based approach)

Most studies report that any CPR is better than no CPR. It is likely that COCPR will be used more often than ventilation/compression CPR. Early CPR (including chest compressions) is associated with better outcomes. Initiating rescue breathing only may delay the commencement of chest compressions. The benefit of chest compressions on ventilation is unclear. The prescribed benefit of COCPR is that it is simpler and therefore more likely to be performed correctly.

In cardiac arrest, a meta-analysis of RCTs (there were three included RCT studies) found chest-compression-only CPR (COCPR) to be associated with increased survival compared with standard CPR (RR 1.22 [1.01–1.46]) *(71)*. In all three included RCTs, randomization occurred at the level of the dispatcher instructing the bystander *(72–74)*. The secondary analysis of observational cohort studies found no difference between COCPR and CPR.

A retrospective cohort (chart review) in New Jersey of out-of-hospital cardiac-arrest patients during resuscitation using paramedic-initiated and medically-directed advanced life support (ALS) algorithms compared cardiac rhythms immediately before and after naloxone administration in 42 patients *(125)*. Of these patients, 42% (n=15) demonstrated some change in their cardiac rhythm. Notably, 19% of all recipients demonstrated changes in cardiac rhythm immediately following naloxone but prior to additional ALS interventions. In addition, 20% of responders

(8% of all subjects) had a post-intervention rhythm sustainable with life. Examples of ECG changes were asystole or pulseless electrical activity (supraventricular tachycardia, ventricular tachycardia or ventricular fibrillation). All 21 non-responders died either in the pre-hospital setting or on arrival at ED. There were 4/15 responders to naloxone that survived to admission, one survival to discharge from hospital. The authors recommend naloxone use in cardiac arrest at any suspicion of opioid over dosage.

There is a theoretical risk of disease transmission with "mouth-to-mouth" assisted breathing, although it is not easily quantified.

Values and preferences

A study in Melbourne of bystander-administered CPR for heroin overdose found CPR was administered in only 9.4% (579/5594 events) of ambulance attendances to heroin overdose *(70)*.

A study in San Francisco of bystander responses to overdose as part of a pilot naloxone-distribution programme reported naloxone administration in 89% of overdose events, with rescue breathing given in 50%. Emergency services were only given in 29% of overdose events *(57)*.

Key concerns about performing CPR (including mouth-to-mouth ventilation) include infectious-disease risk and lack of confidence in their ability to perform CPR correctly *(127–129)*. Assisted ventilation (e.g. mouth-to-mouth) may potentially be less acceptable in circumstance where the victim is unknown or in certain cultures *(129)*. The use of COCPR removes these issues.

A prospective cohort of bystanders in the USA who called an ambulance for cardiac arrest (of any cause, not necessarily related to overdose) reported that individuals with CPR training within five years were more likely to provide CPR than non-trained individuals (OR 4.5, [CI95 2.8–7.3]). Common reasons that the CPR-trained bystanders cited for not performing CPR were:

- 37.5% stated that they panicked
- 9.1% perceived that they would not be able to do CPR correctly
- 1.1% thought that they would hurt the patient.

Only 1.1% objected to performing mouth-to-mouth resuscitation *(130)*. Individuals may be more likely to perform CPR on victims they know *(131)*.

Resource use

Training is required for bystanders to correctly implement CPR. COCPR may be associated with reduced training time and equipment.

Both forms of CPR require few resources. Assisted breathing may require a device to avoid skin to skin contact, such as a sheet of plastic with a hole in it or a mask.

Feasibility

Both forms of CPR were feasible in all studies, notwithstanding cultural issues with mouth-to-mouth resuscitation.

DECISION TABLE: RECOMMENDATION 3

Judgements to inform the decision on the strength of the recommendation

For each of the above recommendations, the following were considered:

Factor	GDG response
Is there high or moderate-quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	No
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes
Are the expected values and preferences clearly in favour of the recommendation? *What is most clear is the values and preferences e.g. people not being comfortable about mouth-to-mouth should be remembered.*	Yes
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes

Strength of recommendation: the GDG decided to set the strength of the recommendation as **'Strong'**.

ANNEX 5
KEY QUESTION 5 – EVIDENCE PROFILE AND DECISION TABLE

Key question 5

What should be the response to opioid overdose after the administration of naloxone and successful reversal of opioid overdose in the community, including by lay first responders?

PICO formulation of key question for evidence synthesis

Population: People with opioid overdose managed in the community setting
Intervention: Observation (for example by transfer to hospital, or staying with the person)
Comparison: No observation (lay first responders) or discharge on-scene (by medical staff)
Outcomes: (see below)

OUTCOMES SELECTED AND RANKED BY GDG FOR KEY QUESTION 5

Outcome	Importance
Overdose mortality	Critical
Overdose complication (such as aspiration)	Critical
Overdose morbidity (prolonged adverse outcome of opioid overdose)	Critical
Aggression directed towards the person encouraging observation by the overdose victim	Critical
Second overdose event within 24 hrs	Critical
Opioid withdrawal reaction to naloxone	Important
Psychosocial intervention / referral to treatment post overdose	Important

Background

Post-resuscitation care refers to the time period immediately following the restoration of spontaneous respiration and circulation following an overdose.

The half-life of naloxone is shorter than that of many opioids. Consequently, post resuscitation care in long-acting overdoses may be prolonged. Additionally, while there is crossover between heroin users and users of prescribed, long-acting opioids, epidemiologically these patient populations do differ.

Evidence to recommendation framework

Summary of evidence

Of the 5594 studies screened, no studies fulfilled eligibility criteria.

Balance of benefits versus risks and harms

A prospective-cohort study designed to determine the clinical characteristics of patients with presumed opioid overdose who could be safely discharged from the ED one hour following the use of naloxone in Vancouver

TABLE 7. OPIOID HALF-LIFE COMPARATIVE TABLE[1,2]

Drug	Plasma half-life (hours)
Short half-life opioids	
Heroin[3]	3–5 min
Morphine	2–3.5
Morphine-6-glucoronide[4]	2
Hydromorphone	2–3
Oxycodone	2–3
Fentanyl	3–4
Codeine	3
Meperidine/pethidine	3–4
Buprenorphine	3–30[5]
Long half-life opioids	
Methadone	24
Propoxyphene	12
Norpropoxyphene[4]	30–40
Normeperidine[4]	14–21
Opioid antagonists	
Naloxone	1–1.5
Nalmefene	8–9
Naltrexone/6-ß-naltrexol[4]	4/13

[1] Active metabolites may prolong pharmacological effects beyond the half-life listed here.
[2] Sustained release preparations alter absorption kinetics to delay time to peak plasma concentration thereby extending clinical effect.
[3] Has active metabolites responsible for perceived longer duration of action.
[4] Active metabolites of other opioids.
[5] Depending on the dose; low doses used for short term analgaesia are typically 0.2–0.3 mg whereas high doses used for opioid dependence are 2–32 mg.

Source: Adapted from *(133)*

included 573 patients in the analysis. A decision-tree rule was developed which predicted safe discharge with a sensitivity of 99% and specificity of 40% *(82)*. The authors stated that patients with presumed opioid overdose can be safely discharged one hour after naloxone administration if they:

- can mobilize as usual
- have oxygen saturation > 92%
- have a respiratory rate between 10–20
- have a temperature between 35.0–37.5C
- have a heart rate of 50–100 bpm
- have a GCS of 15.

Almost all patients in the following several studies that were followed in the analyses after 'discharge-on-scene' refused transportation.

A prospective study linking a pre-hospital emergency care and the forensic examiner's database in Copenhagen over 10 years identified 3245 individuals treated for opioid overdose, 2241 of whom were released on-scene.

Rebound opioid toxicity was identified in three of the 14 deaths recorded within 48 hours of receiving naloxone, which equates to 0.13% of overdoses *(77)*.

There were a number of retrospective studies identified which used cross-linkage of EMS and medical examiner databases to investigate post naloxone for heroin overdose-related deaths.

A retrospective review cross-linking out-of-hospital naloxone administration for opioid overdose and medical examiner databases for opioids as a cause of death over a five-year period in San Diego identified 998 out-of-hospital patients who received naloxone and refused further treatment and 601 medical-examiner cases of opioid overdose deaths. There were no cases in which a patient was treated by paramedics with naloxone within the 12 hours previous to being found dead of an opioid overdose. Two doses of 2 mg naloxone (IV or IM) were administered in 71.5% of cases, three doses in 2.4% *(80)*.

A retrospective review of the management of opioid overdose by emergency medical services in San Francisco reported 575 of 609 (94%) of individuals identified with opioid overdose and having a measurable blood pressure responded to naloxone. Ambulance transfer to hospital was made for 444 (74%) of individuals, and 97% of these were discharged without further intervention. The remaining 3% were admitted for various complications including non-cardiogenic pulmonary oedema, infection and overdoses unresponsive to naloxone (presumed polysubstance overdose) *(81)*. Less than 2 mg of naloxone was administered in only 7% of cases.

A retrospective study of presumed heroin overdoses treated by EMS cross-linked to a cardiac arrest database and medical examiner database in Helsinki identified 145 patients with presumed heroin overdose. There were 84 patients who were not transported to hospital. Of these, 71 had received pre-hospital naloxone (median dose 0.4 mg, 75% < 0.6 mg), eight were given ventilation alone and five recovered spontaneously. All 84 patients had GCS 14 or 15 and showed no signs of hypoventilation. Of the 71 patients who had received naloxone, there were no deaths reported within 12 hours of administration *(78)*.

A retrospective review of EMS and medical examiner databases in San Antonio identified 592 patients treated for presumed opioid overdose who refused further care or transportation. There were no deaths recorded within 48 hours of naloxone administration in this group. There were nine deaths recorded within 30 days of naloxone administration, but the shortest time between naloxone and death was four days *(79)*.

Transfer to hospital may be an opportunity to link with a drug treatment or other health service.

Risks (no observation)

The risk of rebound opioid toxicity following administration of naloxone resulting in death within 48 hours appears to be 0%–0.13% according to several prospective and retrospective data-linkage analyses in high income settings *(77–79, 81, 82, 134)*.

The risk of non-cardiogenic pulmonary oedema is low. An in-hospital case series of 1278 individuals identified 27 patients (2.1%) with non-cardiogenic pulmonary oedema from heroin overdose. Only patients who presented to the hospital were included in the case series *(135)*.

Values and preferences

People who inject drugs may be reluctant to transfer to hospital following an opioid overdose for post-resuscitation care.

Post-naloxone, an individual may have symptoms of acute opioid withdrawal and may be less likely to cooperate with emergency medical services.

Where people who use drugs are subject to stigma and discrimination, individuals having an overdose may be reluctant to attend a health service for post-resuscitation care.

In resource-limited settings, hospital-based post-resuscitation care may be limited.

TABLE 8. CHARACTERISTICS OF OBSERVATIONAL STUDIES – POST RESUSCITATION CARE

Study	Data collection years	Study design	Study setting	Population	Naloxone dose	Discharge criteria	Number of deaths (all cause)	Number of deaths from rebound opioid toxicity	Mortality rate from rebound opioid toxicity
Wampler et al., 2011	November 2007 to June 2009	Retrospective review. EMS dataset included naloxone administered, non-transported opioid ODs cross-referenced to medical examiner's office.	San Antonio, USA	n = 592 7% male Mean age 38 ± 15 years (age range 13–91 years) (7% cardiac arrest, died) n = 552 (93%) received naloxone and not transported.	2 mg IM then 2 mg IV (4 mg total) Further 2mg IM if indicated and consents.	Patient refused transportation post naloxone administration and normal mental status with decision-making capacity, and vital signs within acceptable limits.	0 in < 48hrs post naloxone 9 < 30 days (shortest time post naloxone was 4 days).	0 < 48 hours	0 < 48 hours
Rudolph et al., 2011	1994 to 2003	Prospective. Reviewed medical emergency care unit database, matched to central personal registry cross- referenced to Department of Forensic Medicine database.	Copenhagen, Denmark	n = 2241 patients released on screen following ambulance attended OD.	0.8 mg IV naloxone with 0.4 mg IM addition at discretion of physician.	Treating doctor's discretion (lasting improvements in GSC, oximetry and haemodynamics needed to be present).	14 at < 48 hours	3 < 48 hours	0.13% at 48 hours
Boyd et al., 2006	1 January 1995 to 31 December 2000	Retrospective cohort. EMS patients with suspected opioid overdose, hospital records of transported patients. Cross-referenced to medical examiner and cardiac arrest database.	Helsinki, Finland	n = 145 (transported + non-transported) male 8.28% age 26 (IQR 21 – 32) n = 84 (non-transported to hospital) n = 71 (given naloxone and not transported)	Median naloxone = 0.4 mg (IQR 0.32–0.6 mg) IM/IV/SC	GCS ≥ 14, no hypoventilation.	0 at < 12 hours post naloxone	0 at < 12 hours post naloxone	0 at < 12 hours post naloxone
Vilke et al., 2003	1 January 1996, through 31 December 2000	Retrospective review of records using the San Diego County Quality Assurance Network (QANet) computer database for out-of-hospital providers and the San Diego County Medical Examiner's (ME) Office database.	San Diego, USA	n = 998 (received naloxone and not transported) 83.8% male Mean age 37.7 years (range 16 to 83)	2 mg IM/IV or 4 mg ETT Repeat in no response 1 dose – 26.1% 2 doses –71.5% 3 doses – 2.4%	Answering yes to all the following: 1) Is the patient oriented? 2) Is the patient not impaired by drugs or alcohol? 3) Is the patient competent to refuse care? 4) Have risks and consequences been discussed? 5) Has the patient been advised that medics will return if called back? 6) Has discharge against medical advice (AMA) form been signed?	0 < 12 hours post naloxone	0 < 12 hours post naloxone	0 < 12 hours post naloxone

Where universal health care is not available, costs to the consumer may be associated with post-resuscitation care, influencing desire to attend such services.

Resource use

Discharge on-scene post-naloxone may be less resource intense for emergency medical services and health facilities.

Health facility-based post-resuscitation care is associated with resource availability and service use. The cost of post-resuscitation care to the consumer varies by jurisdiction.

The cost of providing post-resuscitation care in a health facility varies by country and region. Minimal needs might include:

- ability to transfer the patient to a health facility;
- ability to observe and monitor the patient at the health facility in case of opioid toxicity reoccurrence;
- ability to treat reoccurrence of opioid toxicity with naloxone, ventilation and oxygen as necessary.

Lay first responders may be happy to stay with the opioid-overdose person until the period of re-overdose risk is over.

Feasibility

Provision of post-resuscitation care depends on the availability of medical services.
Lay first responders (and health professionals) may not be able to tell the difference between short and long half-life opioids.

DECISION TABLE: RECOMMENDATION 4

Judgements to inform the decision on the strength of the recommendation

For each of the above recommendations, the following were considered:

Factor	GDG response
Is there high or moderate-quality evidence? *The higher the quality of evidence, the more likely is a strong recommendation.*	No
Is there certainty about the balance of benefits versus harms and burdens? *In case of positive recommendations (a recommendation to do something), do the benefits outweigh harms?* *In case of negative recommendations (a recommendation not to do something), do the harms outweigh benefits?*	Yes
Are the expected values and preferences clearly in favour of the recommendation?	Yes
Is there certainty about the balance between benefits and resources being consumed? *In case of positive recommendations (recommending to do something) is there certainty that the benefits are worth the costs of the resources being consumed?* *In case of negative recommendations (recommending not to do something) is there certainty that the costs of the resources being consumed outweigh any benefit gained?*	Yes

Strength of recommendation: the GDG decided to set the strength of the recommendation as **'Strong'**.

ANNEX 6
VALUES-AND-PREFERENCES SURVEY AND KEY-INFORMANT INTERVIEWS

Online survey

In addition to the in-depth interviews below, an online values-and-preferences survey was conducted between 4 February and 20 February. The method was a snowball technique where the initial recipients of the invitation were the meeting participants, WHO collaborating centres and regional offices. There were 661 responses from 45 countries. The survey and its results are available at https://www.surveymonkey.net/results/SM-W7TT3YT/summary.

In-depth interviews

Summary

A values-and-preferences study of people who inject drugs explored the experiences and views of 32 people around HIV prevention, HIV testing modalities, anti-retroviral treatment (ART) for treatment and prevention of HIV, harm reduction and community distribution of naloxone. The study was conducted from January to March 2014 and included 25 members of the PWID community and seven experts or service providers who work closely with this community. Nineteen individuals participated in in-depth interviews, two participants responded by email, due to language restrictions, and 11 individuals participated in a group discussion of the same issues covered in the interviews.

The main findings regarding PWID and community preferences on the pre-hospital management of opioid overdose are summarized in the box below.

The larger issues that influence the potential impact of harm-reduction interventions are poverty, homelessness, mental illness, social exclusion and joblessness.

Community distribution of naloxone should be added to the list of harm-reduction interventions.

Naloxone is a cheap, safe, easy-to-use, life-saving drug. It should be available for community distribution to people who inject drugs, their peers and their families.

Pre-loaded syringes or nasal spray are preferred.

The importance of rescue breathing must be emphasized along with distribution of naloxone.

1. Introduction

One aspect of the WHO guidance-development process involves engaging with communities to understand their values and preferences regarding elements of potential recommendations that will have a direct impact on their lives. Their views and experience are considered along with systematically-reviewed evidence and expert opinion. In this way, guidance can be more responsive to the needs of individuals who are confronting the challenges being addressed by new recommendations and guidance.

This report summarizes the findings of a qualitative study that explored the perspectives and experiences of active drug injectors and former PWID regarding the out-of-hospital management of opioid overdose.

The survey was part of a larger survey conducted to support the development of key population guidelines for HIV prevention and treatment.

2. Methods

An independent consultant conducted the study to ensure impartiality in the interviews and in the analysis of findings. Thirty-five prospective participants – members of the PWID community, experts, activists and service providers – were identified through international and regional networks and invited to participate in semi-structured, in-depth interviews regarding their personal experiences with and perspectives on:

- HIV prevention strategies
- HIV testing modalities
- the use of antiretrovirals for prevention of HIV
- the comprehensive harm-reduction package
- community distribution of naloxone.

Twenty-six people agreed to participate, and 19 people were actually able to participate in interviews, while two respondents provided written answers due to language constraints. In addition, 11 young injecting drug users (ages 16–25) participated in a group discussion of the interview topics led by one of the study participants who works with an organization serving the needs of young homeless people in San Francisco, USA. Those findings are also included in this report, comprising the views of 32 individuals (ages 16–57 years).

Two interview guides were developed in a consultative process with WHO and other experts in the field, one for PWID community members and one for experts and service providers who did not identify themselves as PWID. The different sets of questions reflect a distinction between the values and preferences of PWID community members – the primary focus of this study – and the views of those who work closely with the community but who may not have the same personal experience of the topics covered. Where views of the two groups differ, this is noted. Interviews were 1–1.5 hours in length, and they were recorded with participants' permission. Recordings were used only by the interviewer to facilitate analysis and ensure accuracy of quotes. All participants gave their verbal consent to participate in the study.

Due to the limited number of participants in this study, the content of interviews was not categorized as majority or minority positions. Findings were analysed by assessing the level of support for new interventions being proposed and highlighting areas where positive views were qualified by concerns around ethics, feasibility, acceptability or other issues. Unique views are also included in the report as they contribute important perspectives to the analysis of findings and should be noted in the guidance-development process. Findings are summarized in boxes at the opening of each topic section, and the narrative report reflects the analysis of findings as they emerged in interviews. Direct quotes are used to capture the detail and tone of participants' contributions. However, quotes are not identified by gender or country in order to maintain the anonymity of respondents. Some views are identified by region where conditions and experiences appear to be significantly different from other regions. In general, references are not made to individual countries unless in relation to specific data.

3. Participant profiles

TABLE 1. PARTICIPANT PROFILES BY GENDER AND REGION[1]

	Africa	Americas	South-East Asia	Europe	Eastern Mediterranean	Western Pacific
Women	2	7	—	2	2	2
Men	2	8	3	4	—	—

Note: Age range of participants is 16–57 years.

[1] One service provider from Europe works in Africa; 2 PWID and 1 expert from Europe work with international networks; 1 expert from Western Pacific works with an international network; 11 adolescents and young people who inject drugs (in the USA) contributed views during a group discussion facilitated by a study participant.

TABLE 2. PARTICIPANT PROFILES BY SELF-IDENTIFICATION AND INJECTING DRUG USE[1]

	Member of PWID community	Expert/activist/ service provider
Current injecting drug use	16	*(5)*
Former injecting drug use	9	2 *(7)*
Never used or no answer	—	5

Note: Numbers in parentheses indicate current or former injecting drug users who identify as members of the PWID community as well as experts, activists or service providers for the community.

[1] Two respondents who self-identified as former injectors reported that they are likely to use injecting drugs again in the future; their inputs reflect an ongoing concern about their own access to harm reduction services.

Contributors to this study live in urban areas. Eighteen people work in a wide range of settings:

- community-based services in capital cities and provincial towns;
- international, regional and national networks of PWID (or drug users more generally) based in urban areas in the North and South;
- street-based and mobile services in all regions.

Eleven participants in a group discussion are homeless young people who inject drugs and one participant, affiliated with a university, focuses primarily on research. None of the participants were service providers in public-health settings.

4. Study findings

4.1 Community distribution of naloxone

Key findings regarding community distribution of naloxone are highlighted in the box below.

1) ***Naloxone is a cheap, safe, easy-to-use, life-saving drug.*** *It should be available for community distribution to people who inject drugs, their peers and their families.*
2) *Community distribution of* ***naloxone should be added as an element of the comprehensive harm-reduction package.***
3) ***Pre-loaded syringes or nasal sprays*** *are preferred.*
4) *The importance of* ***rescue breathing*** *must be emphasized along with distribution of naloxone.*

"Naloxone saves lives."

"We deserve to live, to be okay, to have more chances. We have lives of value, we are people, too."

"People are dying every day [here]". The quality of drugs is changing every day because heroin is often not available and so people have to take whatever they can find, and it's very difficult to find the right doses, and so overdose happens all the time. Naloxone used to be more available with Global Fund money and it was so successful, and service providers distributed naloxone in the communities, and it helped a lot and saved a lot of lives. But the Global Fund has not been operating since 2013, now there is [not enough] naloxone."

The discussions of community distribution of naloxone were brief and the views were clear. Thirty-one respondents (one is based in a country where injecting drug use is limited to stimulants, and naloxone was not discussed) expressed unqualified support for making naloxone widely available without prescription and without burdensome conditions. Three respondents acknowledged that overdose is not a significant problem in their settings, however they felt that naloxone should be available to every person who injects opiates.

> *"Availability with prescription (as is the case in many countries) is not enough – it needs to be in the hands of peers, families etc., so that it is easily available."*

Many respondents feel that resistance to making naloxone more widely available to the PWID community and their families and friends can have a dramatic effect in terms of further marginalization of members of the community, reinforcing a sense of alienation from society, which only makes injecting drug users more reluctant to seek and use vital harm-reduction and other health services. In many countries, continued criminalization of PWID also deters peers from getting emergency assistance when someone has overdosed.

> *"There's something so symbolic about naloxone. It's a life-saving intervention. If you say community distribution is not worth [doing], it's a value judgment on our lives."*

> *"What does that say about us if you're willing to let us die when there's such a preventative option in place? [Even if] you oppose harm reduction fundamentally, not being willing to save our lives feels so alien and says so much about what you think about us, and then that affects how we want to engage in services."*

In general, availability of naloxone is variable across regions. In Europe and North America, availability is becoming more widespread but there is not universal access, and it can still be difficult to access naloxone for peer distribution. In most countries where naloxone is legal and available for community use, there are usually conditions that require a prescription and training. In almost all of those cases, only a small amount is given to each person, generally a 2 ml vial, which may be sufficient for one or two doses, depending on the situation. Respondents who mentioned the doses all felt that it would be better to have larger quantities available for community distribution.

Ideally, a sufficient and consistent supply of naloxone for peer workers to distribute along with basic training could create a cascade out to all members of the community. Training must continue to emphasize the importance of rescue breathing. One respondent worries that widespread availability of naloxone could overshadow the critical importance of this overdose management strategy. Another respondent feels that rescue breathing must be designated as preferable to chest compressions which are advised in her setting, but which result in additional trauma (e.g. cracked ribs).

In sub-Saharan Africa and South Asia, availability is much more limited. In most cases, only health professionals are allowed to administer it; in some cases, health providers themselves are not aware of it. In many Eastern Mediterranean countries, naloxone is available only at government health facilities, and only some first responders have access to it. Administration of naloxone requires a doctor's permission, which in turn triggers a report to the police.

> *"Often people will be thrown on the street to die because they are afraid of trouble with the police."*

One respondent in sub-Saharan Africa raised the issue of health information systems as an issue to be addressed when advocating for naloxone.

> *"Current death registration masks the real extent of the problem; death caused by OD is called 'pulmonary embolism', so we don't have the real numbers to use when we advocate for wider distribution of naloxone."*

Arguments against community distribution of naloxone are considered to be baseless.

> *"The main resistance is based on a belief that people will feel safer and engage in more high -risk behaviour and try to get as close to OD as possible, because we have naloxone sitting there. It's a ridiculous argument. It's true, for some users this is part of the game, getting as close as possible without overdosing. But if you know what it's like to go over and then get brought out with naloxone, which is not a pleasant experience, then actually getting your 'stone' right makes much more sense than being reckless, you can enjoy it without being interrupted. The arguments against naloxone just don't add up. And there are complexities to the situation that don't fit with this simplistic assumption that people will act more recklessly (e.g. there may be other substances such as alcohol that are changing the way the body is processing the drug, or a health condition that makes the drug act differently)."*

> *"Dealing with overdose is scary. There are no downsides to having naloxone. We could be saving people's lives! When you work with this community, you lose so many people. People's lives could be saved so easily, it's so easy to administer, it's so logical. The reality is that people hate drug users... and some people feel it's a waste of money if you're using it for drug users."*

When asked if there are any downsides to community distribution of naloxone, one respondent summed up the views of all participants —

> *"None. What kind of question is that?"*

5. Conclusion

There was very strong support from the study participants for the wider availability of naloxone for the management of opioid overdose.

ANNEX 7
COMPOSITION OF GUIDELINE GROUPS

WHO Steering Group

Name	WHO Department
Nicolas **Clark**	Management of Substance Abuse
Vladimir **Poznyak**	Management of Substance Abuse
Annette **Verster**	HIV
Elizabeth **Mathai**	Essential Medicines and Health Products
Margaret **Peden**	Injuries and Violence Prevention
Annabel **Baddeley**	Global TB Programme
Selma **Khamassi**	Service Delivery and Safety

Guidelines Development Group

Name	Gender	Current affiliation	Country of origin	WHO region	Expertise
Robert **Balster** (Chair)	M	Virginia Commonwealth University	United States of America	AMRO	Pharmacology
Barbara **Broers**	F	Hospital University Geneva	Switzerland	EURO	Academic, addiction psychiatry, implementation
Jane **Buxton**	F	University of British Columbia/ BC Centre for Disease Control	Canada	AMRO	Epidemiology, clinical programme management
Paul **Dietze**	M	The Macfarlane Burnet Institute for Medical Research and Public Health	Australia	WPRO	Psychology, addiction research
Kirsten **Horsburgh**	F	Scottish Drugs Forum National Naloxone Coordinator	Scotland, UK	EURO	Programme implementation
Raka **Jain**	F	All India Institute of Medical Sciences – National Drug Dependence Treatment Centre	India	SEARO	Toxicology, pharmacology
Nadeemullah **Khan**	M	Aga Khan University	Pakistan	EMRO	Emergency Medicine and Toxicology
Walter **Kloek**	M	Resuscitation Council of Southern Africa	South Africa	AFRO	Resuscitation
Emran **Razzaghi**	M	University of Tehran	Iran	EMRO	Academic, addiction psychiatry, implementation
Hendry **Sawe**	M	Muhimbili National Hospital	Tanzania	AFRO	Emergency Medicine
John **Strang**	M	King's College London	England, UK	EURO	Academic and Addiction
Oanh **Thi Hai Khuat**	F	SCDI - Center for Supporting Community Development Initiatives	Vietnam	WPRO	Implementation of programmes for people who use drugs

External reviewers

Name	Gender	Current affiliation	Country of origin	WHO region
Sophia **Achab**	F	University Hospital of Geneva	Switzerland	EURO
Luis Isidoro **Alfonzo Bello**	M	Pan American Health Organization	United States of America	AMRO
Sawitri **Assanangkorchai**	F	Prince of Songkla University	Thailand	SEARO
Marc **Augsburger**	M	The International Association of Forensic Toxicologists	Switzerland	EURO
Regis **Bedry**	M	European Association of Poisons Centres and Clinical Toxicologists	France	EURO
Scott **Burris**	M	Tempe University School of Law	United States of America	AMRO
Edward **Day**	M	Birmingham Medical Trust	England, UK	EURO
Gail **D'Onofrio**	F	Yale School of Medicine	United States of America	AMRO
Ali **Farhoudian**	M	Substance Abuse and Dependence Research Centre	Iran	EMRO
Evgeny **Krupitsky**	M	St Petersburg Psychoneurological Institute	Russia	EURO
Soraya **Mayet**	F	Durham University	England, UK	EURO
Dasha **Ocheret**	F	Eurasian Harm Reduction Network	Lithuania	EURO
Shahin **Shadnia**	M	Shahid Beheshti University of Medical Sciences	Iran	EMRO
Sharon **Stancliff**	F	Harm Reduction Coalition	United States of America	AMRO
David **Sugerman**	M	Centers for Disease Control and Prevention	United States of America	AMRO
Ambros **Uchtenhagen**	M	Addiction Research Institute	Switzerland	EURO
Alexander **Walley**	M	Virginia Commonwealth University	United States of America	AMRO
Sharon **Walsh**	F	University of Kentucky	United States of America	AMRO

ANNEX 8
DECLARATIONS OF INTEREST

Guidelines development group

Name	Current affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
Robert **Balster** (Chair)	Virginia Commonwealth University	Yes; 6e	January 2001 received an honorarium for serving as a consultant on medication development to Reckitt Benckiser. Co-Director of International Programme in Addiction Studies which receives funding for scholarships from Reckitt Benckiser through Virginia Commonwealth University. Does not receive any personal support from Reckitt Benckiser. 20% of salary is paid by an Intergovernmental Personnel Agreement with the U.S. Agency for International Development for work as a science advisor.
Barbara **Broers**	University Hospital of Geneva	None	
Jane **Buxton**	University of British Columbia/BC Centre for Disease Control	None	
Paul **Dietze**	Macfarlane Burnet Institute for Medical Research and Public Health	Yes; 2b, 5a	Travel support of approx. US$ 1500 from Australian Capital Territory Health Directorate.
Sergii **Dvoriak**	Ukrainian Institute on Public Health Policy	None	
Kirsten **Horsburgh**	Scottish Drugs Forum	Yes; 1a	Annual salary of £37 000 for employment as National Naloxone Coordinator at Scottish Drugs Forum, post fully funded by Scottish Government.
Raka **Jain**	All India Institute of Medical Sciences, New Delhi	Yes; 1b, 2a, 2b	Funding of USD $28 498 from UNODC (ROSA) whilst co-investigator in project on effectiveness of oral substitution with buprenorphine and to establish a protocol developed for oral substitution with buprenorphine. Honorarium from UNODC (ROSA) whilst co-investigator on prevention of spread of HIV amongst vulnerable groups in South Asia for rolling out opioid substitution therapy in prison settings. Funding of US $24 444 from AYUSH, MOH & FW, Government of India whilst co-investigator on effectiveness of yoga in patients of opiate dependence. Funding of approx. US $99 930 and honorarium from UNODC(ROSA) whilst co-investigator on effectiveness and feasibility of methadone in patients of opioid dependence. Funding of US $26 135 from Rusan Pharmaceuticals whilst co-investigator on Post marketing surveillance of methadone in India. Funding to India, AIIMS, New Delhi, of US $129 476 for project on efficacy of varenicline for smokeless tobacco use. Funding of approx. US $26 666 from Indian Council of Medical Research while principal researcher on feasibility of transporting urine samples of drug users on filter papers for screening drugs of abuse: a pilot exploratory study. Funded approx. US $27 777 from Indian Council of Medical Research whilst principal investigator on effect of nalbuphine on opiate withdrawal in rats: behavioural, biochemical and molecular study.
Nadeem Ullah **Khan**	Aga Khan University	None	
Walter **Kloeck**	University of the Witwatersrand	None	
Emran M **Razaghi**	Tehran University of Medical Sciences	None	

Name	Current affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
Hendry Robert **Sawe**	Muhimbili National Hospital	None	
John **Strang**	Kings College, London	Yes; 1b, 2a, 2b	Kings College receives £1500/month from Martindale during period of advice on a safety and pharmacokinetics PK study of a new rapid-absorption formulation of buprenorphine which has been developed by Martindale. Provides expert consultancy opinion on the trial and analysis for review of the clinical trial protocols for the trial, review of the clinical expert report on the trial and participation as an independent expert in review meetings. £600 000 approx. to clinical trials office from Martindale for investigation of the same new formulation of buprenorphine developed by Martindale. Organizing a new random trial in UK of a long-acting naltrexone implant versus oral naltrexone versus placebo with recently detoxified opiate addicts. Trial is fully funded by NIHR but has received implants at no cost from manufacturer and is preparing placebo implants at a modest cost. No payment has been made to Kings College, John Strang or NHS. In early stages of studying pharmacokinetics and efficacy of possible non-injectable naloxone formulations at Kings College.
Oanh **Thi Hai Khuat**	Center for Supporting Community Development Initiatives (SCDI)	Yes; 6b	I work for a local NGO whose mission is to improve quality of life of marginalized populations, including drug users. If WHO releases such a guideline, it would benefit greatly drug users in countries like mine, and would make our work much easier in saving lives.

Consultants to the GDG

Name	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
Margaret **Harris**	None	N/A
Rebecca **McDonald**	None	N/A
Nick **Walsh**	None	N/A
Anna **Williams**	None	N/A

External reviewers

Name	Current affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
Sophia **Achab**	University Hospital of Geneva	None	
Luis Isidoro **Alfonzo Bello**	PAHO	None	
Sawitri **Assanangkorchai**	Prince of Songkla University	None	
Marc **Augsburger**	The International Association of Forensic Toxicologists	None	
Regis **Bedry**	UHSI, Hospital Pellegrin	None	
Scott **Burris**	Temple University,	Yes; 5a, 5b	In my capacity as a professor of law and public health, I testified before the legislature of Colorado when it was considering drug overdose legislation. As a member of a community coalition in my home state of Pennsylvania, I have spoken to legislators, reviewed legislative text, and written published opinion pieces supporting overdose legislation including naloxone.
Edward **Day**	Kings College London	None	

Name	Current affiliation	Competing interest declared?	Nature of declared competing interest (as expressed in declaration of interest form)
Gail **D'Onofrio**	Yale University School of Medicine, Department of Emergency Medicine	None	
Evgeny **Krupitsky**	St.-Petersburg Bekhterev Research Psychoneurological Institute	None	
Dasha **Ocheret**	Eurasian Harm Reduction Network	Yes; 1a	EHRN was funded US$ 7200 per year in 2011/12 from Open Society Foundations partly dedicated to advocacy of overdose prevention and naloxone distribution among people who use drugs – salary was partly covered by grant.
David **Sugerman**	U.S. CDC	None	
Shahin **Shadnia**	Shahid Beheshti University of Medical Sciences	None	
Sharon **Stancliff**	Harm Reduction Coalition	None	
Ambros **Uchtenhagen**	Swiss Research Institute for Public Health and Addiction, affiliated with Zurich University	Yes; 1b	Participation in a consultation seminar of WHO Geneva in February 2014 for the preparation of the guidelines.
Alexander **Walley**	Clinical Addiction Research and Education Unit, Boston University School of Medicine	Yes; 1b, 2b	Funding of $1000 in 2012 from Social Sciences Innovation Corporation for a NIDA SBIR grant to develop an online module for overdose prevention among first responders. Approximately $5000 reimbursement and honoraria for four trips for travel and lecturing on overdose prevention and naloxone rescue in Michigan and Washington DC for Open Society Foundations, Drug Policy Alliance. Salary support from the Boston Medical Center whilst working as principal investigator on a CDC Injury Centre grant to study the impact of overdose prevention programmes on opioid overdose-related deaths in Michigan.
Sharon **Walsh**	University of Kentucky	Yes; 1b, 2b	Travel reimbursement US$ 3000 since 2010 from PCM Scientific (funding provided to PCM through unrestricted educational grant from Reckitt Benckiser and RB had no involvement in development - content was not related to overdose or overdose prevention. Served as Chair (3 yrs) and speaker (4 yrs) at Improving Outcomes for the Treatment of Opioid Dependence. Received an average of $5800/yr. whilst chair and $1500 whilst speaker only. Requested and was supplied by Reckitt Benckiser a small supply of drug and matching placebo for a buprenorphine product for a study supported by an independent grant from National Institute of Health (U.S.)
Soraya **Mayet**	Durham University	None	

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An estimated 69 000 people die each year from opioid overdose, which is easily treatable with naloxone and basic resuscitation techniques, a treatment that is usually only available in ambulances and hospital settings. Most opioid overdoses are witnessed, often by someone known to the person who has overdosed, such as a friend, family member or professional whose work brings them into contact with people at risk of overdose. This guideline makes specific recommendations for health services to work with such lay persons who are likely to witness an opioid overdose, to enable them to treat opioid overdose in an emergency situation and prevent further opioid overdose deaths.

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