

# BMJ Open NTNU intranasal naloxone trial (NINA-1) study protocol for a double-blind, double-dummy, non-inferiority randomised controlled trial comparing intranasal 1.4 mg to intramuscular 0.8 mg naloxone for prehospital use

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## ABSTRACT

**Introduction** Intranasal (IN) naloxone is widely used to treat opioid overdoses. The advantage of nasal administration compared with injection lies in its suitability for administration by lay people as it is needless. Approved formulations of nasal naloxone with bioavailability of approximately 50% have only undergone trials in healthy volunteers, while off-label nasal sprays with low bioavailability have been studied in patients. Randomised clinical trials are needed to investigate efficacy and safety of approved IN naloxone in patients suffering overdose. This study investigates whether the administration of 1.4 mg naloxone in 0.1 mL per dose is non-inferior to 0.8 mg intramuscular injection in patients treated for opioid overdose.

**Methods and analysis** Sponsor is the Norwegian University of Science and Technology. The study has been developed in collaboration with user representatives. The primary endpoint is the restoration of spontaneous respiration  $\geq 10$  breaths/min based on a sample of 200 opioid overdose cases. Double-dummy design ensures blinding, which will be maintained until the database is locked.

**Ethics and dissemination** The study was approved by the Norwegian Medicines Agency and Regional Ethics Committees (REC: 2016/2000). It adheres to the Good Clinical Practice guidelines as set out by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Informed consent will be sought through a differentiated model. This allows for deferred consent after inclusion for patients who have regained the ability to consent. Patients who are unable to consent prior to discharge by emergency services are given written information and can withdraw at a later date in line with user recommendations. Metadata will be published in the Norwegian University of Science and Technology Open repository. Deidentified individual participant data will be made available to recipients conditional of data processor agreement being entered.

## Strengths and limitations of this study

- In this trial, an approved high-concentration/low-volume formulation of naloxone designed for intranasal (IN) administration is investigated.
- Patients studied are treated for opioid overdose and primary endpoint, the return of spontaneous respiration is clinically relevant.
- The aim is to investigate if IN naloxone is non-inferior to 0.8 mg intramuscular naloxone.
- The trial is not powered to detect differences in less common adverse events.
- Unlike Take Home Naloxone for lay people, antidote is administered by emergency service professionals in this trial.

**Trial registration numbers** EudraCT Registry (2016-004072-22) and Clinicaltrials.gov Registry (NCT03518021).

## INTRODUCTION

The ongoing opioid overdose epidemic has increased the interest for the main opioid antagonist naloxone. Take Home Naloxone (THN) programmes are now common in many countries,<sup>1</sup> with naloxone often administered via the intranasal (IN) route. Many of the formulations of naloxone were improvised for IN use, but were never designed for IN use. They were actually solutions for injection that were sprayed into the nose.<sup>2</sup> The volumes administered were far above the recommended 0.1–0.2 mL level, ideal for systemic uptake of the drug through the nasal mucosa.<sup>3</sup> The bioavailability of injection solutions administered through the nose has been found to be as low as 11%,<sup>4</sup> implying that low-volume solutions with higher concentrations

are needed to deliver a therapeutic dose. Despite these shortcomings, epidemiological studies<sup>5</sup> and a few clinical trials<sup>6–9</sup> have shown promising results of such improvised IN naloxone. The WHO pointed out the low evidence behind many nasal sprays used in naloxone programmes and called for clinical trials on this crucial issue.<sup>10</sup> From the first mention of THN programmes in 1996, it took 20 years for naloxone formulations with regulatory approval to become available in the market.<sup>2 11</sup> However, these formulations are approved on the basis of pharmacokinetic studies in healthy volunteers alone,<sup>12–14</sup> and none of them have been tested in clinical studies of patients with opioid overdose.

Previous trials in patients have shown nasal spray to be inferior to intramuscular (IM) naloxone.<sup>6–9</sup> This is not surprising as these studies used dilute formulations of IN naloxone such as 0.4 mg/2 mL,<sup>8</sup> 0.8 mg/1 mL<sup>9</sup> or 2 mg/1 mL.<sup>6 7</sup> Because of limitations in the nasal mucosal uptake, such doses are expected to provide far less systemic exposure than the commonly administered intramuscular dose of 0.8 mg. In the current NTNU intranasal naloxone trial (NINA-1), the IN naloxone dose is 1.4 mg/0.1 mL, which is equipotent with an intramuscular dose of 0.8 mg in preclinical studies on healthy volunteers.<sup>14</sup> The 1.4 mg dose of nasal spray holds marketing authorisation in 12 European countries. This is the first clinical trial to test an approved formulation in the wide prehospital field. The objective of this paper is to describe the methodology of the ongoing trial.

## METHODS AND ANALYSIS

The NINA-1 protocol was designed using the Norwegian Clinical Research Infrastructure Network templates,<sup>15</sup> written according to Standard Protocol Items: Recommendations for Interventional Trial guidelines<sup>16</sup> and will be reported according to the Consolidated Standards of Reporting Trials guidelines.<sup>17</sup> The sponsor is the Norwegian University of Science and Technology (NTNU). The study is a two-center, double-blind, double-dummy, phase III, randomised controlled trial. It has a non-inferiority design, as we consider 0.8 mg intramuscular naloxone to be a safe and efficient first dose in the management of deeply intoxicated opioid overdoses outside the hospital. Endpoints are described in [box 1](#) Patients are included at two sites through the ambulance services at Oslo University Hospital and St. Olavs hospital, Trondheim University Hospital, both in Norway.

### Participant selection

The ambulance staff will assess patients prior to randomisation for inclusion based on the following criteria (see [box 2](#)):

Patients who are not administered in the study drug are treated according to local protocol and treatment guidelines, which involves ventilatory support and administration of naloxone intramuscularly 0.4–2.0 mg.<sup>18</sup>

## Box 1 Study endpoints

### Primary endpoint

- ▶ The proportion of participants with a return of spontaneous respiration ( $\geq 10$  breaths/min) within 10 min of administering the study drug.

### Secondary endpoints

- ▶ Time from administration of naloxone to respiration  $\geq 10$  breaths/min.
- ▶ Changes in oxygen saturation and level of consciousness measured by the Glasgow Coma Scale.
- ▶ Suitability of the spray device in a prehospital setting.
- ▶ Overdose complications.
- ▶ Opioid withdrawal reactions.
- ▶ Adverse reactions to the naloxone formulation.
- ▶ Need for rescue naloxone.
- ▶ Rebound opioid intoxication within 12 hours of inclusion.
- ▶ Reasons not to give rescue naloxone to non-responders.
- ▶ Follow-up after care.

## Sample size and plan for statistical analyses

The number of overdoses needed to demonstrate that IN naloxone was not inferior to intramuscular naloxone and was calculated to be 200. This was based on the assumed probability of patients responding to the standard treatment (0.8 mg intramuscular naloxone)  $p_{IM} = 0.88$ . The inferiority margin was set to  $\Delta = 0.15$ . The choice of margin was a result of wide discussion and based on our observational studies and clinical experience. The null hypothesis that the proportion of responders receiving IN naloxone,  $p_{IN}$ , is smaller than the proportion of responders receiving IM naloxone

$$H_0 : p_{IM} - P_{IN} > \Delta.$$

## Box 2 Participant selection

### Inclusion criteria (all criteria to be met)

- ▶ Spontaneous respiration  $\leq 8$  breaths/min.
- ▶ Glasgow Coma Scale score  $< 12/15$ .
- ▶ Miosis.
- ▶ Palpable carotid or radial arterial pulse.

### Exclusion criteria (at least one criterion present)

- ▶ Cardiac arrest.
- ▶ Failure to assist ventilation using bag-mask technique.
- ▶ Facial trauma, epistaxis or visible nasal blockage.
- ▶ Iatrogenic opioid overdose.
- ▶ Suspected participant aged  $< 18$  years.
- ▶ Suspected or visibly pregnant participant.
- ▶ Participant who has received naloxone by any route in the current overdose.
- ▶ Participant in prison or custody by police.
- ▶ Emergency medical staff without training as study workers.
- ▶ No study drug available.
- ▶ Study drug frozen as indicated by the Freeze Watch in the kit or past its expiry date.
- ▶ Deemed unfit for inclusion due to any other cause by the study personnel at the scene, such as an unsafe work environment for the emergency medical staff.

The alternative hypothesis is that IN naloxone is non-inferior to intramuscular naloxone

$$H_A: p_{IM} - P_{IN} \leq \Delta.$$

A two-sided significance level of 5% and a power of 90% are assumed. The upper bound of the CI of  $p_{IM} - P_{IN}$  shall not exceed  $\Delta$  to reject  $H_0$  and claim non-inferiority of IN naloxone. During the study period, there is a possibility that the same individual may have more than one overdose and be included more than once in the trial. However, the number of overdoses per individual is expected to be low and one episode for most individuals. If the same individual receives the same treatment on multiple occasions, this could reduce the power of the study to a certain extent. However, if the individual is allocated to different treatment groups on different occasions, this could potentially improve the power of the study. Since the probability of receiving each treatment is 50% on each occasion, the probability of receiving different treatments on two occasions is 50%, and thus we expect this to approximately balance out during the course of the study.

The primary endpoint will be analysed using a logistic regression model, adjusting the treatment variable for the study center. From the model, the predicted average marginal means of the proportions in the treatment groups will be calculated while properly adjusting for the within-subject covariance due to repeated overdoses in the same individuals.

Dichotomous secondary endpoints will be analysed as the primary endpoint, while continuous secondary endpoints will be analysed by mixed linear models or appropriate non-parametric alternatives. Primary and secondary analyses will be based on the patients who fully comply with the prespecified treatment strategy (the 'per-protocol' population). Sensitivity analyses will be performed based on all patients who receive the study medication. Prior to database lock, all statistical analyses will be prespecified in a detailed statistical analysis plan.

### Randomisation and blinding

The Clinical Trial Unit at Oslo University Hospital will perform a computer-generated block randomisation with random block sizes stratified by center and a 50/50 randomisation to each study arm.

To ensure blinding, a double-dummy design is used. Participants are administered both a nasal spray and an intramuscular injection at the same time, of which one contains naloxone and the other an inactive substance. This ensures that all patients receive naloxone and that both the patient and study workers are blinded for the treatment which the patient is allocated. The drugs will be administered as simultaneously as possible, and within 30 s of each other. The IN spray is administered first if unable to coordinate simultaneous administration on site. The fixed sequence of administration of both was chosen to ensure uniformity and simplify training. The study drug kits are numbered according to the randomisation

list, and the kit number becomes the participant study number for later unblinding. Each participating ambulance only holds one kit at the time, thus ensuring that the ambulance staff does not perform randomisation at the scene. There is no serial order in which the boxes are used as they are in many ambulances at the same time.

The blinding will be maintained throughout the study until after database lock. The trained coders who enter the data from the ambulance records and case report forms, investigators who assess adverse events and monitors and study statisticians will treat the participant data by the inclusion number only and remain blinded. The data monitoring and safety committee (DMSC) obtains access to unblinded data through their own statistician. After database lock, the data will be unblinded.

### Study drugs

The investigational medicinal product (IMP) is a 1.4 mg naloxone hydrochloride nasal spray. This drug is administered as 1.4 mg/0.1 mL nasal spray using the Aptar Unit Dose Device (Louveciennes, France). The formulation and its pharmacology are extensively described in the literature.<sup>14 19-21</sup>

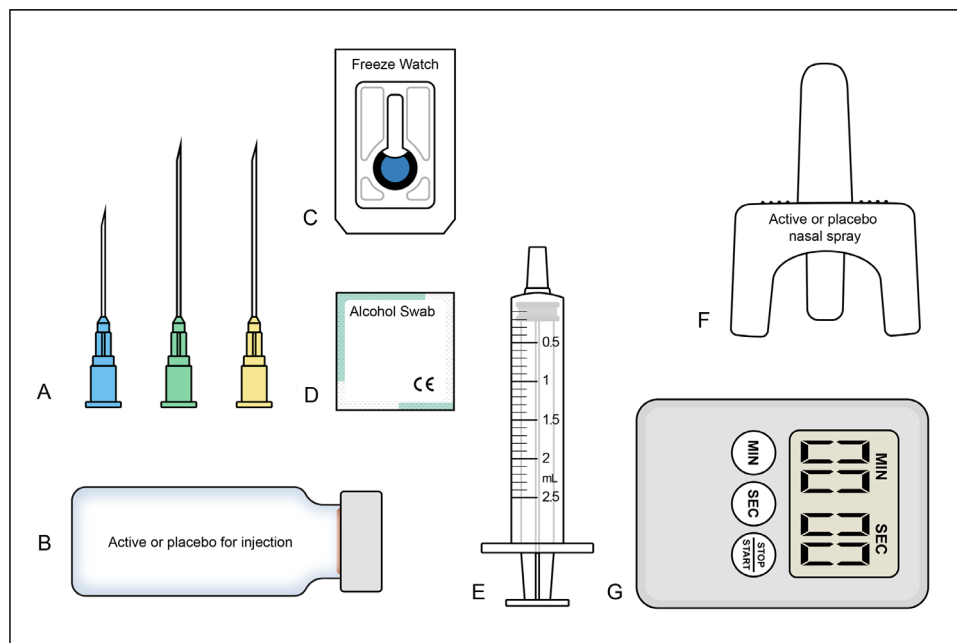
The active comparator is 2 mL naloxone hydrochloride (0.4 mg/mL), with a total dose of 0.8 mg. The intramuscular injection should be given in the deltoid muscle.

The IN placebo is similar to IMP, with the exception that the placebo holds no naloxone hydrochloride. The intramuscular placebo is 2 mL of 9 mg/mL sterile sodium chloride for injection. Vials for injection are similar, and both are blinded and labelled for use in clinical trials.

Both active and placebo nasal drugs are described in IMP dossiers and are approved for use in this trial. Nasal drugs are produced by Sanivo Pharma, Oslo, Norway. The blinding of vials and sprays, assembly, randomisation of kits and labelling are performed by the hospital pharmacy of the Central Norwegian Regional Health Authority at St. Olavs hospital, which holds a manufacturer's authorisation for human IMPs.

### Kit description: key treatment and study tool

The study kit is a sealed A5 size cardboard box that holds active or placebo IN study drug and active or placebo intramuscular study drug in a polystyrene foam casing, as illustrated in [figure 1](#). All kits contain active naloxone as either an IN or intramuscular formulation. The kit also contains a stopwatch to measure time to the primary endpoint, case report forms for trial documentation, information letters to participants for consent and indicator of exposure to frost and syringes. Study workers use 23G×30 or 21G×50 mm hypodermic needle for intramuscular injection, the larger for bigger patients. A 19G×40 mm needle was provided for aspiration of liquid for intramuscular injection from vial. The seal should only be broken with the intention of including a patient, and the seals must be inspected prior to inclusion. A system for accounting each study kit is in place. To administer study drug, the staff went through a study-specific online



**Figure 1** Study kit contents. (A) Hypodermic needles for aspiration and intramuscular administration. (B) Active or placebo for intramuscular injection. (C) Freeze watch. (D) Alcohol swab. (E) Syringe, 2.5 mL. (F) Active or placebo nasal spray. (G) Stopwatch illustration by Øystein Horgmo, Oslo University Hospital.

teaching module and half-day live scenario-based training session. This included training on consistency in delivering IN and intramuscular drug and other study-specific procedures. To assess respiratory rate at time of inclusion, staff were instructed to manually count at least 8 s with no spontaneous ventilation in a patient with a free airway, this short interval does not delay respiratory support. After 10 min, the number of breaths were counted for 60 s.

### Trial procedures

All patients are approached with airway, breathing and circulation treatment (figure 2). Patients fulfilling the inclusion and exclusion criteria are treated with medication from the study kit and provided ventilation support using bag-mask technique. The emergency medical staff should continue to ventilate the patient and monitor the clinical response, measuring respiration and level of consciousness. Ambulance staff should note the number of minutes from the administration of the study medicine to a spontaneous respiration rate of  $\geq 10$  breaths/min. If the patient does not respond adequately for the primary endpoint or does not wake up after 10 min, additional naloxone (non-IMP) and other treatment as per local protocols should be provided. Non-IMP naloxone can be administered at any time if the patient's state deteriorates or for any other reason deemed necessary by the ambulance crew.

### Procedure for obtaining consent

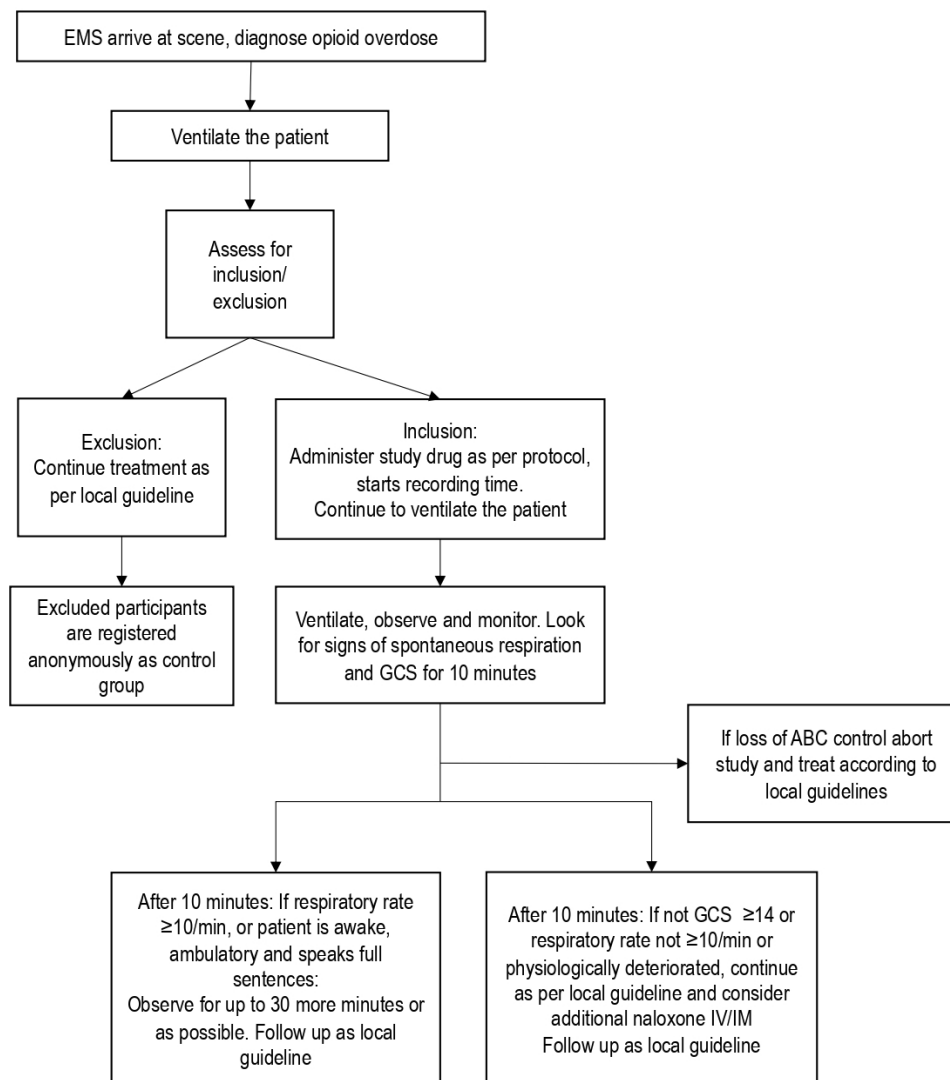
The consent procedure is differentiated with several paths open to participants (figure 3), depending on their ability to receive information and make judgements at the time of treatment. Since randomisation and treatment occurs prior to any possible consent, the actual

consent is whether they agree to be registered in the study database. Participants who regain consciousness and have the ability to give consent are informed by study workers and asked for permission to use the data registered in the trial. This deferred consent is given orally and documented by two trained study workers. Participants who do not respond to naloxone or are not able to give informed consent at the scene are given written information and a chance to withdraw online or by telephone in the future. Participants who are not able to give oral consent at the time of the overdose and do not contact the study team will be included in the study. The consequence of consent not given is that all identifying data and data on response to effectiveness endpoints are deleted from the study. Safety data will be recorded in an anonymised database. Safety data include adverse events and the need for rescue naloxone. Recurrence is not recorded as this is incompatible with anonymisation of data. This anonymised registration is performed to prevent bias in safety reporting. Excluded patients who were screened for inclusion are registered with demographic data and are registered in an anonymised database.

The written information given to patients includes a short description of the intervention and the study with their unique study number. The webpage [www.nalokson.no](http://www.nalokson.no) holds more information and a webform for withdrawal. Participants can also withdraw by telephone. This procedure and all the written information were approved by the ethics committee and translated into English, Polish, Romanian and Somali.

### Safety procedures

A study telephone line has been set up. The study workers can contact a member of the trial working group 24 hours



**Figure 2** Flow chart for study visit. ABC, Airway, Breathing, Circulation; EMS, Emergency Medical Services; GCS, Glasgow Coma Scale; IM, intramuscular; IN, intranasal.

for any questions, concerns and reports with respect to serious adverse events (SAEs). In case of SAEs or other safety concerns, an emergency unblinding procedure of individual study kits is in place.

### Adverse events

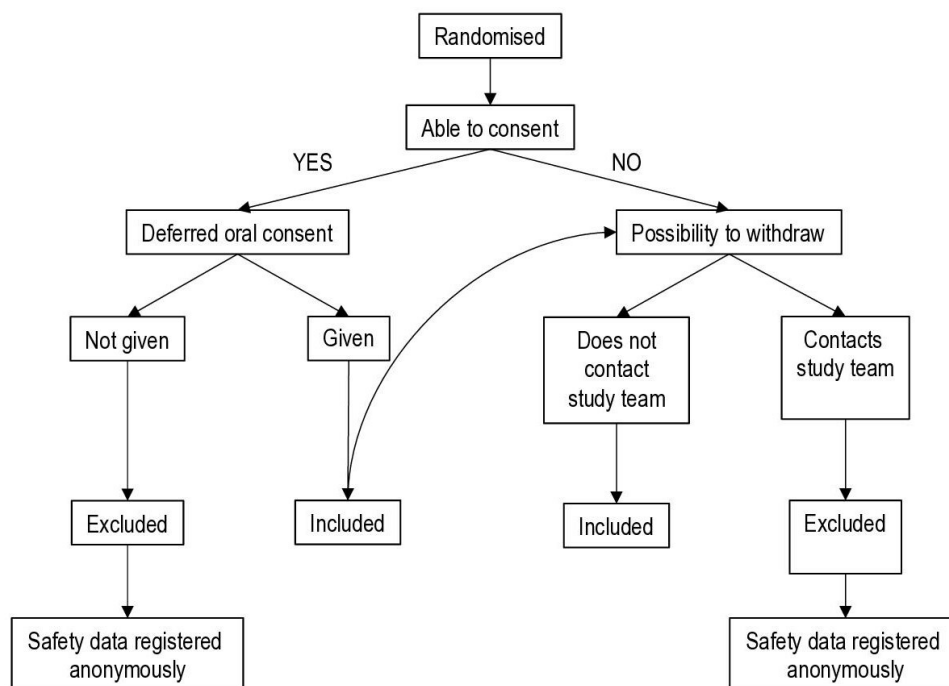
Participants should be observed particularly for adverse events and opioid withdrawal reactions. The Good Clinical Practice (GCP) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and GCP-ICH definitions of adverse events and SAEs apply. Expectedness is described in the study Investigators' Brochure to guide if SAEs shall be classified as suspected unexpected serious adverse reaction or not. All adverse events will be assessed and coded according to the Medical Dictionary for Regulatory Activities and will be reported in the clinical study report. All included patients will be checked for rebound opioid intoxication within 12 hours after inclusion through the electronic medical dispatch center system at each site.

### Data collection and study monitoring

Data are collected from ambulance records, the dispatch center callout system and study-specific case report forms. Data are manually entered into an electronic data management system (Viedoc, Uppsala, Sweden) from paper-based charts by trained study assistants and investigators. All study-related information will be stored securely at the study site. A risk-based data monitoring procedure is in place. This allows for clinical trial monitoring by the Clinical Trials Unit of Oslo University Hospital that fulfils regulatory requirements and ICH-GCP guidelines, without the need for 100% source data verification of the patient data. The procedure involves performing a risk analysis to identify high-risk elements of the study concerning patient safety and primary endpoint data.

### Patient and public involvement

The consent procedures and the information material have been developed in cooperation with a user participation board. The board was established in the design



**Figure 3** Flow chart over procedure for consent.

phase of the trial and has been involved in all phases of preparation and application to relevant authorities. The board consists of former and current drug users, representatives from the main drug user organisations and from organisations for the families of drug users. The board will also be instrumental in the continuing dissemination of information throughout the recruitment period and for communicating the results once published.

#### Data monitoring and safety committee

An independent DMSC is recruited and oversees the study with preset check points, at 20 and 100 included participants. The DMSC will review recruitment, data quality, protocol deviations, safety and adverse events. The committee has access to unblinded safety data, monitoring reports and reported protocol deviations through a designated statistician. The DMSC will not review data or perform interim analysis on the primary endpoint.

#### Discussion

IN naloxone has the potential to save lives but can also harm already vulnerable patients. The extensive use of undocumented medical interventions, both in patient treatment and as public health measures, is questionable and debated.<sup>22 23</sup> The optimal route of administration, dose and concentration of naloxone needed to safely revive patients in respiratory arrest, without eliciting opioid withdrawal symptoms, remains unknown. The NTNU has developed the naloxone nasal spray at 1.4 mg/dose and designed the NINA-1 trial to try to balance and investigate all these concerns.

#### Non-inferiority design and inferiority margin

A study design with comparison of IN naloxone against placebo/no treatment was considered unethical, given the well-known effects of naloxone and its importance in the treatment of opioid overdose. The advantages of IN naloxone compared with those of intramuscular naloxone are ease of administration, particularly for lay people, with no risk of exposure to injury from needles or sharps. Based on this, a non-inferiority design is ideal to establish that the new drug is not inferior to the existing treatment. The NINA-1 trial has chosen a non-inferiority margin of 15% difference as an acceptable level. Naloxone is a drug that needs titration, and repeated dosing is encouraged to ensure effectiveness without triggering acute withdrawal. In this setting, a non-inferiority margin of 15% seems reasonable and this margin has been used in other clinical studies comparing the similarities between drugs for the same indication.<sup>24</sup>

#### Route of administration, concentration and dose

The study drug in NINA-1 has marketing authorisation in 12 European countries. The dose of 1.4 mg naloxone hydrochloride (1.26 mg naloxone) was chosen based on extensive pharmacokinetic studies in healthy volunteers to match the 0.8 mg intramuscular dose.<sup>14 19-21</sup> Other approved nasal naloxone sprays have used 0.4 mg intramuscularly as the comparator in healthy volunteer studies.<sup>12 13</sup> We have chosen 0.8 mg intramuscularly, based on local experiences that this dose is sufficient in 88% of overdose cases and is the most commonly used dose in patients with severe opioid intoxication. The comparator dose of 0.8 mg intramuscularly was also used in a recent clinical trial of overdoses in an Australian safe injection

facility.<sup>9</sup> An advisory committee to the the US Food and Drug Administration has advised that a dose above 0.4 mg is the most appropriate comparator.<sup>25</sup> The WHO recommends intramuscular doses not to exceed 0.8 mg as the first dose in community overdose.<sup>10</sup>

### Patient selection and setting

Respiratory arrest is the cause of death in opioid overdoses, and the restoration of spontaneous breathing was therefore chosen as our primary endpoint. By including patients with severe symptoms only, we aim to show non-inferiority of the 1.4 mg spray in the patient cohort at the highest risk of a fatal outcome of opioid intoxication. By recruiting widely through prehospital emergency services, we aim to reduce selection bias. The Oslo site is expected to recruit the majority of cases. The Oslo city center ambulance station has a safe injection facility in its catchment area. The most commonly used illicit opioid in Norway is heroin. Although a range of other opioids are misused, fentanyl analogues play a minor role in the current Norwegian drug market.<sup>26</sup> With this design there may be fatal rebound opioid overdose within 12 hours that are not registered as we are not able to link the study database to the Norwegian Cause of Death Registry, thereby underestimating recurrence.

### ETHICS AND DISSEMINATION

The main treatment of opioid overdose is ventilation, administration of antidote and follow-up to prevent rebound opioid intoxication and new overdose. The only treatment option that is altered in this trial is the route of administration and dosage of the first dose of naloxone.

Studies on patients in emergency medicine are recognised to pose particular challenges in research, with informed consent being a major concern. As in many jurisdictions, the Norwegian law gives exemption to the condition of informed consent prior to inclusion in emergency settings, with certain conditions.<sup>27</sup> Opioid users may be considered a particularly vulnerable group. The Declaration of Helsinki describes research and protection in vulnerable participants, and concludes that research should meet the health needs or priorities of this group.<sup>28</sup> This has guided the design of the NINA-1 trial, with the aim of maximising opportunity to give informed consent, and at the same time include patients during emergency treatment. Active user participation and community consultations were part of the design of the study and are still ongoing. The consent procedure balances the rights of all included participants to refuse registration in the database and the need to collect safety information on the intervention to reduce bias and maximise the safety of a new medicine. The consent procedure reflects the fact that patients are likely to have a different clinical state after inclusion in the study. Some will have regained both consciousness and the ability to give informed consent, while others will remain unconscious and need urgent transport to a hospital and emergency medical

follow-up. Few participants are also likely to be without a registered postal address or telephone number and may be difficult to contact after the treatment intervention. Patients treated for life-threatening respiratory arrest outside of the hospital are usually admitted to a hospital for further treatment and follow-up. Patients treated for opioid overdose with naloxone are known to be an exception to this rule, with patients remaining at the scene of the overdose or leaving the emergency department.<sup>29</sup> The present consent flow chart (figure 3) reflects the various states of the participants and intends to maximise the opportunities for participants to give or withdraw consent. In addition to oral information at the scene of the overdose, written information is available both as simple forms handed out and as more comprehensive information online. To compensate for a signature and written consent, oral consent must be documented by two certified study workers. Similar consent procedures, with a mix of deferred consent, waiver of consent and other forms have been seen, for example, in previous research on out-of-hospital cardiac arrest.<sup>30 31</sup>

### Trial status

This article is based on protocol V.3.3. dated 6 March 2020. The first patient was included on 12 June 2018, and data collection is to be completed by the end of 2020.

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**Contributors** AKS and OD are the main authors of this article, with all other authors participating in the writing process and structuring of this article. OD was the national coordinating investigator from 31 October 2016 to 1 May 2019 with AKS holding that position until present. A-CB is the principal investigator at the Oslo site. SM was the principal investigator at Trondheim Site from 31 October 2016 to 1 May 2019 with JD holding that position from 1 May 2019 until present. IT and FH are investigators and members of the executive trial committee. MV is the study statistician. All authors have reviewed and accepted the latest submitted version of the manuscript.

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**Competing interests** The contents and production of study kits are funded by dne pharma as, Oslo, Norway. Norwegian University of Science and Technology (NTNU) and its subsidiary Technical Transfer Office have signed cooperative and licensing contracts with dne pharma as to seek commercialisation of this nasal naloxone formulation. This regulates potential royalties for OD through NTNU. dne pharma as has compensated OD for business travel from Trondheim to Oslo and to Lisbon. AKS spoke at a seminar arranged by dne pharma as in Lisbon in October 2019 without an honorarium or other compensation. The other authors declare no conflicts of interest. The funding sources have no role in the study design, data collection, data analysis, data interpretation or writing of the clinical study report.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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